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APRIL, 1928

ORIGINAL ARTICLES.

HYPERTENSION HEART.*

GEORGE FAHR, M.D.,

MINNEAPOLIS, MINN.

(From the Department of Medicine, University of Minnesota.)

WHEN a child was born to parents in the eighteenth century they could expect it to live until it was thirty-nine years of age, that being the average age of survival at that period. At the present time, parents can look forward to an average length of life for their children of about fifty-five years. This increase in the average length of life has been brought about largely by the control of the epidemic and endemic diseases due to microörganisms, such as smallpox, typhoid fever, tuberculosis, diphtheria, and so forth, and by a better hygiene for the infant. On the other hand, the adult who survives until the age of forty-five today cannot expect to live much longer than did his eighteenth century forbears of the same age.[1] In fact, Pearl states that "during 2000 years man's expectation at birth has been steadily improving while at the same time his expectation of life at advanced ages has been steadily worsening." Hyperpiesia† or the high-blood-pressure disease, cancer, coronary

* Address delivered before the Minnesota State Medical Society, Duluth, 1927.

† I have used the term "hyperpiesia" instead of "essential hypertension," "vascular hypertension," "chronic interstitial nephritis" or "Bright's disease" in piety to Sir Clifford Allbutt, who deserves the credit for insisting that there is a condition of high blood-pressure not associated with nephritis and who named this disease hyperpiesia. Hyperpiesia is usually associated with some degree of arteriolarsclerosis of the smallest renal arteries. In some cases the degree of vascular degeneration in these small arteries is very intense and there may be a large number of vessels involved. Under these circumstances a considerable amount of renal damage may result from anemic necrosis and in about 10 per cent of all cases may be so extensive that an insufficient number of functioning glomeruli is left and renal insufficiency and uremia close the scene. As a rule the amount of renal arteriolar disease is very moderate and renal insufficiency plays a very negligible rôle. These latter cases die of heart failure (55 to 55 per cent) or stroke (35 to 40 per cent).

arteriosclerosis and cerebral arteriosclerosis stand before the threshhold of the fifth decade to prevent any marked increase in longevity. The greatest of these opponents of longevity is hyperpiesia. I have calculated from the mortality statistics for the registration area of the United States for 1924 that approximately 140,000 deaths in persons fifty years of age and older are due to hyperpiesia, wholly or in part.* This is as great as the combined death rates for cancer, all forms of tuberculosis and all forms of respiratory disease including pneumonia, for the same age category and year, and twice as great as the death rate for cancer. Romberg reckons that 45 per cent of all hyperpiesia cases die of heart failure, 45 per cent of apoplexy and 10 per cent of uremia. We reckon that 50 to 55 per cent die of heart failure, 35 to 40 per cent die of apoplexy and 10 per cent die of uremia. Hypertension heart or the heart failure associated with high blood pressure thus becomes the most common form of heart failure and the most important result of high blood pressure continued over many years. We shall confine ourselves to a discussion of the heart failure consequent upon long-continued high blood pressure.

If we use Romberg's figure of 45 per cent for the percentage of cases of hyperpiesia dying of heart failure, we reckon that approximately 63,000 persons, fifty years or older die of hypertension heart in the United States every year. But if we use our figure of 50 per cent for the number of cases of hyperpiesia dying of heart failure we calculate 70,000 deaths in persons fifty years of age or over from hypertension heart in the United States for the year 1924. We can calculate roughly in another way, the approximate death rate from hypertension heart in persons over fifty years of age in the United States. Fifty per cent of all the cases of organic heart disease in patients over forty-five years of age coming to the Cardiac Clinic of the Univ[illegible]ity of Minnesota Dispensary have a systolic blood pressure 180 [illegible]m. or over and a diastolic of 100 mm. or over, the greater majority being over 200 systolic and 120 diastolic. The mortality statistics for 1924 give 140,000 deaths for heart failure in persons over fifty years of age. Using our incidence of hypertension hearts at the Cardiac Clinic for the calculation we figure out 70,000 hypertension heart deaths in persons over fifty years of age. However, not all persons who have heart failure symptoms associated with high blood pressure finally die of heart failure. A few will die of apoplexy but the number dying of apoplexy who have heart failure will be small according to our experience and there are two-thirds as many more cases with high blood pressure but no cardiac failure symptoms and signs coming to this dispensary clinic, many of whom will ultimately develop heart failure. For this reason we believe our figure of 70,000 deaths from hypertension heart in persons over fifty years of age is a minimum figure insofar

* See Appendix.

as a calculation from our own data and the heart failure statistics of the mortality tables is concerned. Moreover, the vital statistics for 1924 give 65,000 deaths from chronic nephritis in persons over fifty years of age. I have already assumed on very good grounds that at least 32,000 of these cases were really chronic high-blood-pressure cases not associated with true glomerulonephritis but with arteriolar sclerosis of the renal vessels of various degrees.* Many of these deaths were certainly not due to true uremia but rather to heart failure. Therefore, our figure of 63,000 to 70,000 deaths from hypertension heart should probably be raised considerably by these cases listed under chronic nephritis.

There are variations of the magnitude of 10 to 15 per cent in these figures, but despite these errors the figures give the order of magnitude of death from hypertension heart very well. We can say that the death rate for persons over fifty years of age from hypertension heart is now about 70,000 a year. The death rate from primary valve defect, the death rate from luetic aortitis, and the death rate from coronary sclerosis unassociated with hypertension all fall below this figure. I[2] have shown that approximately 70 per cent of all chronic heart-muscle disease not associated with primary valve defect or luetic aortitis, is associated with high blood pressure. These figures are sufficient to show the great importance of hypertension heart.

What have we been calling this heart failure consequent upon high blood pressure in the past? This disease has undoubtedly existed since the beginning of time. Probably the majority of these cases have been classified by practising physicians as chronic myocarditis, this being a very common term for that type of heart failure which is primarily due to failure of the heart muscle and unassociated with organic valve defect. Much of this so-called chronic myocarditis has been attributed to infection from chronic foci in abscessed teeth, chronic sinusitis, badly infected tonsils, and the like. The term chronic myocarditis has been a very unhappy one as it has turned the attention of physicians away from the cardinal features of chronic heart-muscle disease. Many of these cases are diagnosed mitral insufficiency because about 80 per cent of all cases of hypertension heart exhibit a moderately loud to loud systolic murmur at the apex, and well transmitted to the axilla. In fact many of these cases have a relative mitral insufficiency due to the marked left ventricular dilatation and stretching of the mitral ring. But the mitral insufficiency is a consequence of the heart failure rather than its cause, though we must concede that when the mitral valve becomes incompetent the heart failure is augmented by this new and unfavorable factor. Frequently hypertension heart is designated hypertrophy and dilatation of the heart. There

* See Appendix.

is no other objection to this term, which rightly describes the condition, than that it is equivocal. In mitral stenosis, aortic insufficiency and in congenital heart disease there is also hypertrophy and dilatation of the heart. The term cardiorenal disease is also frequently used to name the condition of hypertension heart. Frequently there is extremely little arteriolar sclerosis found in these kidneys at postmortem, and renal insufficiency except as consequent upon the heart failure is not very common. For this reason, we object to the term cardiorenal disease. Many cases of so-called "beer heart" have been proved by examination of the kidneys to be hypertension hearts, for the kidneys showed various degrees of arteriolar sclerosis of the finer vessels. Sometimes hypertension heart is called arteriosclerosis or arteriosclerotic heart. Many physicians still believe that arteriosclerosis is commonly a cause of high blood pressure. Modern clinical and pathologic investigation has shown that there can be marked large vessel and medium-sized vessel arteriosclerosis without high blood pressure. Moreover, many cases of known high blood pressure show very little or no arteriosclerosis of the palpable vessels. Nor does arteriosclerosis in itself increase the work of the heart.[3] The term arteriosclerotic heart should be reserved for cases with coronary arteriosclerosis.

What are the findings in the hypertension heart at autopsy? First of all they are nearly always large hearts, varying in weight from 400 gm. to 750 gm., the normal heart weighing between 250 and 350 gm. The increase in weight is due to hypertrophy. This hypertrophy is largely confined to the left ventricle though many cases show some hypertrophy of the right ventricular musculature also. In many of these hearts the muscle is normal in every way, excepting for the increase in volume of the individual fibers. Other hearts show myocardial fibrosis. The hypertension hearts showing myocardial fibrosis usually show arteriosclerosis of the coronary vessels and Clawson[4] believes that his studies demonstrate that fibrosis of the myocardium in hypertension hearts is only found where coronary sclerosis is also present. Bell[5] has found that only 10 per cent of all hypertension hearts show no coronary arteriosclerosis at all, 55 per cent show a moderate degree of coronary sclerosis, and 35 per cent show a moderately severe to severe degree of coronary sclerosis. A few of these hearts show a slight degree of fatty degeneration of the heart muscle fibers but the number of cases is very low in our experience.

What is the story of the development of heart failure in hypertension? Many cases of hyperpiesia give no symptoms during the early years of the disease. The high blood pressure creeps up insidiously and may be found only on a routine examination, the patient being very much surprised to know that he has high blood pressure, having considered himself or herself exceptionally healthy and vigorous. Some cases come to the physician early with symptoms

of dizziness, of vague pains in the neck, of headaches, of fullness in the head, and other symptoms unimportant in themselves. In my experience, the high blood pressure does not commonly cause symptoms of heart failure until many years have elapsed unless the case is complicated by moderately severe or severe coronary arteriosclerosis or the individual is engaged in severe physical work.

I now have records of a number of cases followed year after year with blood-pressure readings taken every few months and can state definitely that persons may have blood pressure well over 200 systolic for twelve to fifteen years before developing definite symptoms of heart failure. Let me cite four of my best-followed cases.

Case I was found to have a blood pressure of 220 systolic in April, 1912, at which time he had been working extremely hard and had a very serious financial situation to worry him. Becoming very nervous and showing a faint trace of sugar in his urine, he was sent to a celebrated consultant who discovered the high blood pressure. From that time until the present (1927) he has been examined at frequent intervals by many physicians. After a vacation or a "cure" in a spa his blood pressure will be found as low as 170 to 190 systolic and 110 to 115 diastolic. Otherwise the systolic blood pressure is always 210 to 230 and the diastolic 115 to 130. This patient has always worked very hard as an executive and business man but has taken very little physical exercise other than a moderate amount of walking. At present, at the age of seventy-four years, he still works hard in his various businesses and only notices shortness of breath on walking rapidly, climbing stairs, and the like. The heart shows a definite dilatation to the left on examination with the orthodiagraphic method; ml = 10.5 cm., mr = 3.5 cm., transverse thoracic = 26.5 cm.* The patient's height is 5 feet 6 inches and weight is 160 pounds. The liver is just below the costal margin in the right midclavicular line. There is slight edema of the ankles when on his feet for a long period. At times there are moist râles at both bases. This past year I discovered pulsus alternans on one occasion. One can sum up this case by saying that after fifteen years of very high blood pressure a moderate degree of cardiac failure has slowly developed.

Case II has been well followed for eleven years. I have seen her at monthly to bimonthly intervals for six years. She has had three hospital periods of study; two simply for study of the case and for the purpose of testing out the value of various types of treatment and one because of severe heart failure. The blood pressure has been as high as 300 systolic. It has always been between 220 and 260 systolic in the six years during which I have studied her excepting when at rest in bed, at which time the blood pressure will fall to 160 to 180 systolic. The diastolic ranges from 120 to 140. One year and a half ago, and after at least ten years of very high blood pressure, she came to see me in a state of severe decompensation. Previously her heart had been regular. There was auricular fibrillation present when she presented herself in heart failure. She had been out on the road as a saleswoman and had developed a "cold." Immediately, she noticed severe shortness of breath, swollen legs and pain over the upper abdomen. She hurried back to Minneapolis because she wished to enter

* This is a definite enlargement for his size and chest diameter. The teleroentgenogram taken at six feet shows a transverse diameter of 15.4 with an increase of about 9 mm. in the past year. The Roentgen ray report contained the diagnosis "hypertension or aortic type of heart."

the University Hospital. She presented a classical picture of heart failure, edema of the lungs, edema of the lower extremities, enlarged tender liver, marked dyspnea, totally irregular and unequal pulse. After a long rest in bed and digitalis she was allowed to leave the hospital. She has given up all work excepting a little housework. She walks only for short distances when shopping or coming to the Dispensary. Under these circumstances, she has had no return of severe decompensation. She gets short of breath only if she exerts herself. Her heart was dilated moderately to the left (telerentgenogram) before her severe heart failure, now it is a typical "boot"-shaped heart in an advanced stage of dilatation. Before her severe decompensation, she had noted a gradual increase in weakness and shortness of breath on exertion during the last two years before the onset of the severe heart failure.* Teleroentgenogram of her heart taken at intervals of a year show a slow but progressive dilatation during the last six years. The teleroentgenogram taken at 6 foot distance shows now ml = 12.0 cm., mr = 5.1 cm., T = 17.1 cm., transverse thoracic = 24.5 cm. The orthodiagram, which is, of course, the exact measurement, gives ml = 11.0 cm., mr. = 4.2 cm., T = 15.2 cm. and the transverse thoracic measurement 23.0 cm. The orthodiagram represents a dilatation of about 4 cm.

Case III is only forty-seven years of age. She has been followed in the University Dispensary and by one private physician for eight years. During this time the blood pressure has never been under 240 systolic or 120 diastolic. It has been higher. I have seen her at intervals of one or two months for six years. She has been studied on two occasions in the University Hospital. The blood pressure has never come down below 240 systolic and 120 diastolic on long continued rest in bed, Allen salt-free diet, alkaline diet, or any other form of treatment tried on her. The blood pressure remains the same while she is sleeping. At present an orthodiagram only shows a slight left ventricular dilatation, ml = 9.1, cm., mr. = 4.3 cm., T = 14.0 cm., transverse thoracic diameter = 24.0 cm. (see Fig. 1.) Up until a year ago she had no symptoms which could be interpreted as suggesting myocardial weakness. Now she finds she tires easily and is slightly short of breath when she walks fast or climbs stairs rapidly. She does her own housework and cannot be called an invalid in any sense whatsoever, at the present time. Typical heart failure is on its way but has not yet developed into its severe form as yet in her.

Case IV—I have one other case who has been followed at frequent intervals in the University Hospital and Dispensary for ten years and who at present only shows mild dyspnea on exertion. Her blood pressure was 230 systolic and 100 diastolic in the University Hospital in 1917, and the systolic has never been under 200 in the past ten years, usually it has been 220 to 230. The diastolic has ranged between 110 and 130 in the Dispensary records. Her orthodiagram recently showed ml = 11.0 cm., mr = 5.0 cm., T = 16.0 cm., transverse thoracic = 24.0 cm. This corresponds to a dilatation of about 4 to 5 cm. in transverse diameter. Her electrocardiogram showed left preponderance in 1917. This patient has done very little hard work during the past ten years, which is probably one reason why she is not yet suffering from severe heart failure.

These cases used as illustrations are not at all isolated cases in my series. I have a number of cases, which are at present cases of severe heart failure or moderately severe heart failure, who give a

* Recently she went through a severe upper respiratory infection. After many weeks' rest in bed she now appears little the worse for it.

history of blood pressures over 200 systolic ten or twelve years previously. I have followed some of these cases for five or six years at intervals and am sure of their blood pressure readings throughout this period. The blood pressure readings previous to my taking over the cases are not as reliable as in the above 4 cases because they were given to me by the patients from memory and are not from case records. In the 4 illustrative cases, the previous records are from the case records of doctors of the University Dispensary.

Undoubtedly the muscle of the left ventricle hypertrophies and thus receives an increased ability to do work. There are men engaged in strenuous athletics who have blood pressures of 200 systolic and over in my collection. I have seen one gentlemen of fifty-five years whose blood pressure has been over 200 systolic for at least two years before my examination and who did not want to give up such strenuous exertion as is implied in tennis playing,* bag punching, and tumbling, despite the fact that of late he has noticed greater breathlessness on severe exertion than formerly. On my examination his blood pressure was 200 systolic and 120 diastolic. The latest report this summer states he still plays tennis now and again. There are men carrying on the strenuous work of lumbermen in our northern forests with blood pressures well over 200 systolic and 120 diastolic without noting any marked shortness of breath or other signs of heart failure, although it is true that on questioning they admit that they find it harder to do the work they could formerly perform with great ease and that they notice that they "puff" hard when the work is fast or especially heavy, and tire very easily. How many years they can do this my case records do not show, but it has been my impression that high blood pressure combined with severe physical exertion gives a much shorter prognosis than high blood pressure associated with more or less sedentary life. All the cases collected by me with records of high blood pressures continued over ten or more years are found in persons who did not work hard with their muscles.

If the patient with high blood pressure escapes apoplexy, uremia or an intercurrent death from other cause, he surely develops heart failure ultimately. Usually the patient notices tiring at his work first. He cannot accomplish as much as previously because he tires easily. If he hurries or climbs stairs he notices definitely he is getting short-winded. Slowly or sometimes suddenly dyspnea develops. In some patients the first signs of heart failure are smothering spells at night. Perhaps as many as 5 per cent of all cases first call a doctor for these attacks of noctural dyspnea. Others have noticed some shortness of breath but do not come to a doctor

* He is a very excellent tennis player and plays a good hard game. In fact, whatever he does, he does with great expenditure of energy.

until they discover some edema about the ankles at night. There are other cases which have come to a physician when a sense of fullness or pain in the upper abdomen due to a large passive congested liver, or bloating and belching of gas after meals probably associated with portal stasis, makes them think they have "stomach trouble." A few come because of palpitation of the heart and on examination a dilated left ventricle, and the signs of heart failure are discovered. In our experience shortness of breath is the most common symptom bringing these patients to the physician.

According to the postmortem examinations of Dr. E. T. Bell[6] only 10 per cent of hypertension hearts have no demonstrable coronary arteriosclerosis. About 55 per cent show a very moderate degree of arteriosclerosis of the coronaries, sufficient at times to produce some anatomic change in the heart muscle and undoubtedly a very moderate handicap for the efficient beating of this overworked left ventricle. Thirty-five per cent of all hypertension hearts have moderately severe to severe arteriosclerosis of the coronary vessels. In these cases, there is often very definite degeneration of part of the heart muscle with fibrosis consequent upon the necrosis of the muscle fibers, and in these hearts the obstruction to normal volume of bloodflow through the heart muscle is a serious handicap to the efficient working of the overworked heart muscle.

It is, therefore, not strange that as many as 5 per cent of all hypertension hearts give a history of angina pectoris, either in its classic form or in less typical but none the less definite forms. Hypertension hearts do not carry on as long where there is a combination of very high blood pressure and moderately severe to severe coronary sclerosis. In these cases we have a combination of fatigue from increased heart work, and decreased ability of the heart to do work in consequence of reduced circulation and the destruction of muscle fibers that is associated with coronary sclerosis. The electrocardiogram in these cases often shows a negative T in Leads I or II, or splitting and prolongation of the *Q–R–S* group or low voltage or bundle-branch block, signs frequently associated with coronary sclerosis. Where no coronary sclerosis or only slight coronary sclerosis is present, the electrocardiogram usually shows only a left preponderance. Sometimes the electrocardiogram shows nothing abnormal.

The most characteristic physical sign of hypertension heart with the exception of the high blood pressure is the left ventricular dilatation. The left ventricle of the heart in hyperpiesia dilates sooner or later and we get a characteristic "soek"-shaped or "sabot"-shaped outline on percussion and on Roentgen ray examination.* Fig. 1 is the latest Roentgen ray of the heart of Case No. III taken at a distance of 6 feet from the target of the tube. This shows a

* During the first years of hypertension there may be no demonstrable dilatation. Dilatation comes on gradually and is the earliest sign of failing heart.

moderate dilatation of the left ventricle exclusively. Formerly I taught that only aortic disease or hypertension led to this shape. Now I know that occasionally when neither aortic disease or hypertension are present this shape will develop in cases of coronary sclerosis, especially of the left descending branch. If the heart has not the "mean" normal shape to start with, we may not get the "sabot" shape after dilatation. Fig. 2 is the teleroentgenogram of the heart of a patient whose blood pressure is 210 systolic and 100 diastolic and has been in the Minneapolis General Hospital twice with decompensation of a very mild degree. There is undoubtedly some dilatation of the left ventricle present in this heart but the shape is far from the "sabot" shape. This is because the heart was a "drop"-shaped heart to begin with. In our experience such hearts take on a nearly normal form when left ventricular dilatation takes place in aortic regurgitation or hypertension. Sometimes the heart in hypertension takes on the shape of the heart in Fig. 3. This is the teleroentgenogram of the heart of a patient whose blood pressure was 200 systolic and 120 diastolic in severe decompensation in 1917. This teleroentgenogram was made in 1922 at a time when the blood pressure was 190 systolic and 130 diastolic during decompensation and one and a half years before death. As there was no autopsy permitted, we do not know whether coronary sclerosis was present in this heart. We believe that there are two causes for this shape which represents both left and right ventricular dilatation. In the first place, whenever the blood pressure rises above normal there must be some increase in left intraventricular pressure and as the left ventricle fails this intraventricular pressure must rise more. This must ultimately lead to increased work for the right ventricle. In the second place as the left ventricle dilates a time must arrive when relative mitral insufficiency develops. There will be individual variations in the length of time necessary for the development of relative mitral insufficiency and there will be individual variations in the degree of this insufficiency. When the insufficiency is marked, there will be increased work for the right heart. Sooner or later the right heart will dilate. The degree of right-heart dilatation determines whether a pure "sabot" form or a modified form develops resembling more or less the heart of mitral disease. It usually is not difficult to differentiate between the heart in primary mitral disease and the heart in hypertension with relative mitral insufficiency. In hypertension the left ventricular dilatation is much more pronounced than the right ventricular dilatation. There is usually a suggestion of the "sabot" shape still remaining in the hypertension heart with relative mitral insufficiency and right-ventricular dilatation.

A systolic murmur, loudest at the apex and transmitted to the axilla, is heard in at least 80 per cent of all hypertension hearts with decompensation. The accentuation of the pulmonic second

is not pronounced as in mitral valvular disease. Because of the accentuation of the second aortic sound and its loudness the intensity of the second pulmonic sound is relatively faint. The shape of the heart, the high blood pressure, and the lack of accentuation of the second pulmonic serve to differentiate hypertension heart from mitral disease. Auricular fibrillation is not an uncommon finding in hypertension heart. In fact, many of these hearts carry on fairly well until auricular fibrillation sets in. Extrasystoles are occasionally present. Heart block is practically never found unless there is a high degree of coronary sclerosis. Gallop rhythm occasionally develops when severe decompensation sets in. It is usually of grave significance. Pulsus alternans is found more frequently in hypertension heart than in any other form of heart disease in my experience. It does not always mean serious failure. I have seen it appear three to five years before death in heart failure. Under these circumstances, it is not present at all examinations.

Blood-urea nitrogen and nonprotein nitrogen are often moderately increased (40 to 60 mg.) in decompensation in hypertension heart. This increase in blood urea is more frequently found in hypertension heart than in any other form of heart disease in decompensation. This is not to be wondered at. Often there is considerable renal arteriolar sclerosis and some destruction of the renal glomerulotubular units in hyperpiesia of some years' standing. With part of the renal secretory mechanism damaged, it is not strange that some decrease in ability to secrete urea develops when heart failure sets in. This moderate increase in blood urea in the blood does not signify clinical uremia. Most of the cases of hypertension heart do not develop outstanding symptoms of uremia.

The most characteristic sign of hypertension heart is the high blood pressure. It is really remarkable to see extremely high pressures held up during severe heart failure to within a day or two of death. Recently I observed a case of hypertension heart in severe decompensation at the Minneapolis General Hospital in which the blood pressure was 250 systolic and 160 diastolic twenty-four hours before death. At autopsy the 650 gm. heart showed only the very slightest coronary sclerosis. This is not an isolated case by any means. The blood pressure remains aboye 200 systolic and 120 diastolic in many of the cases up to within a few days of death in heart failure. I have seen high blood pressure in cases of mitral stenosis (proved at autopsy) up to within twenty-four to forty-eight hours of death in heart failure! I have seen blood pressures of 220 systolic in aortic regurgitation of luetic aortitis origin and in aortic regurgitation due to valve defect (arteriosclerotic) up to within forty-eight hours preceding death! I have observed that where there is severe coronary sclerosis the blood pressure has a greater tendency to fall as heart failure develops than where there is no coronary sclerosis, or very slight coronary sclerosis. But

not all cases of hypertension heart with coronary sclerosis show reduced blood pressure. At times, cases of hypertension heart and coronary sclerosis retain elevated blood pressures until within a few days before death.

Sometimes one gets the impression that the onset of auricular fibrillation tends to lower the blood pressure though cases with auricular fibrillation may have very high pressures up to within a few days of death. Sometimes the blood pressure will fall in a case of hypertension heart from no apparent cause. In this case the patient may be given an added number of years to live because of the lessening of the work of the heart. Let me give an example. This case was in the University Hospital in 1917 with decompensation and a blood pressure of 200 systolic and 120 diastolic at the time of severest decompensation. His blood pressure when in the University Hospital in severe decompensation in 1920 was not recorded. In 1922, 1923 and 1924, he was in the Minneapolis General Hospital on seven different occasions with symptoms of decompensation and a blood pressure which varied between 160 systolic and 90 diastolic and 190 systolic and 130 diastolic in 1922, between 140 systolic and 90 diastolic and 170 systolic and 110 diastolic in 1923, and between 122 systolic and 80 diastolic and 150 systolic and 90 diastolic in 1924. In 1923 and 1924, the blood pressures were usually between 130 systolic and 80 diastolic and 140 systolic and 90 diastolic so that the blood pressure was really only very slightly elevated. The degree of decompensation could not explain the decrease in blood pressure for this was apparently not any more marked than in 1917 when the blood pressure during severest heart failure was high. Between 1920 and 1922, auricular fibrillation had appeared and definite peripheral arteriosclerosis (gooseneck radials) had become apparent. These two factors may have been the cause of the reduction in blood pressure. On the other hand, his electrocardiogram suggested coronary sclerosis and this may have been a factor tending to lower his pressure. The patient died suddenly at the General Hospital. It was impossible to get an autopsy to confirm the diagnosis of coronary disease.

Probably continued rest in bed is the most potent factor in reducing the blood pressure in many hypertension heart cases. Rest in bed will often bring down high blood pressure quite a little, not infrequently nearly to normal, and it is possible that the enforced bed-rest in heart failure is a most important factor in lowering the blood pressure in these cases. One can not exclude the diagnosis of hypertension heart because the blood pressure is not elevated at the time of examination. It may have been elevated for years but because of rest in bed, coronary sclerosis, auricular fibrillation, heart failure or a combination of all of these factors the blood pressure at the time of examination may be only slightly elevated or not elevated at all. Examination of the retina with the ophthalmoscope

will help in making the diagnosis in such cases. The eye grounds of patients with hypertension heart practically always show signs of generalized and local vascular narrowing, compression of veins by arteries, increased tortuosity, more intense, metallic light-streaks along the arteries, and occasionally also "hard" white spots, all of which are good evidence for renal arteriolar sclerosis and, therefore, of long-continued high blood pressure.

We must say a word about the effect of acute infections in these cases and about the effect of chronic foci of infection. The effect of severe acute infections upon these hearts is undoubtedly a very deleterious one while the infection lasts. A severe acute infection may at any time arise to finally push over into severe decompensation a heart just struggling along under its burden, and once the heart decompensates it may never return to compensation or be only unstably compensated. Sometimes auricular fibrillation seems to date from the onset of a severe acute infection and once started it does not subside. An infection may lead to thrombi in the auricles from which emboli may result. A severe acute infection may bring about death in a patient with a heart already in severe decompensation.

In attempting to evaluate the effect of chronic foci of infection upon the hypertension heart, we must remember that we are dealing with infections, which, if they exist, are quantitatively very much less severe than acute severe infections such as bronchopneumonia, lobar pneumonias, erysipelas, acute upper respiratory infections, and so forth. Therefore, it would seem logical that the effect of the toxins absorbed from chronic foci of infection or the bacteria emigrating from these foci into the blood stream must be cumulative if definite harm is to be ascribed to these foci.

I have seen patients with heart failure in hypertension hearts develop serious lobar pneumonias, erysipelas, "grippe," and so forth, and yet when they had finally weathered the storm and had had a long bedrest I could not determine by either clinical or instrumental examinations that they were very much the worse for having had these severe infections. In these patients at least, the effects of the severe infections upon the myocardium seemed only temporary. Such cases have made it hard for me to understand how minute infections of teeth, tonsils, etc., even when prolonged, can injure heart muscle very greatly unless acute rheumatic endocarditis or myocarditis are developed. According to Aschoff and Tawara,[7] the hearts of cases of hypertension which are not associated with old-rheumatic-valve defect or recent acute endocarditis show practically no signs of inflammatory or toxic processes in their muscle. In this connection, I might cite Case IV above. This patient came to the University Hospital for the first time in 1917, not because of her high blood pressure but because of frequent sorethroats. She would not allow removal of her tonsils on this occasion. She

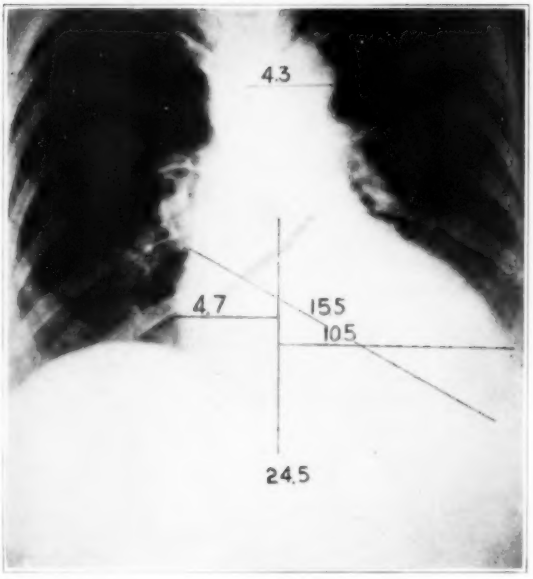

FIG. 1.—Teleroentgenogram of heart of case No. III. Blood pressure, 240 systolic, 120 diastolic for at least eight years. No marked clinical symptoms or signs of heart failure. Moderate left ventricular dilatation. "Sock"-shaped heart.

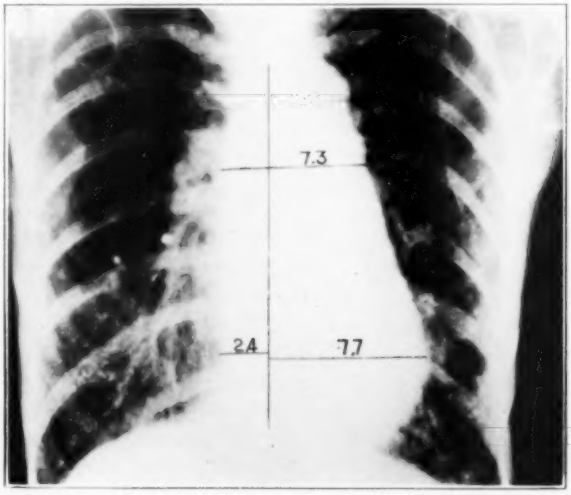

FIG. 2.—Teleroentgenogram of heart of patient with blood pressure, 210 systolic, 100 diastolic. Taken after compensation of moderate degree of heart failure. Moderate dilatation of "drop" heart.

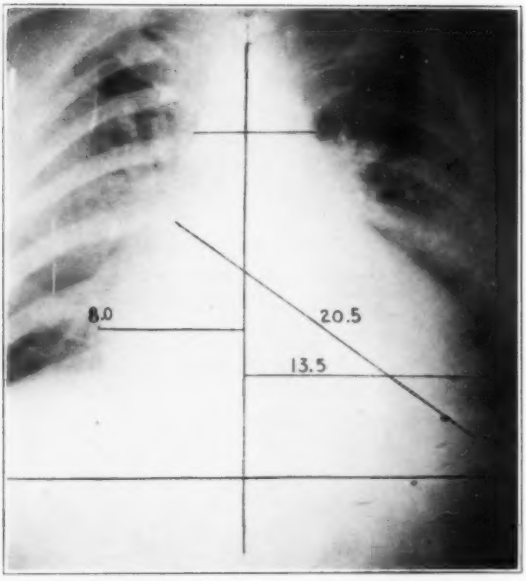

FIG. 3.—Teleroentgenogram of heart of patient with hypertension and cardiac failure of five years' duration. Shows marked left ventricular dilatation and moderate right ventricular dilatation. No longer typical "sock" shape.

finally consented to tonsillectomy five years later, during which period she had suffered from frequent attacks of tonsillitis. These five years of bad tonsils with high blood pressure seem not to have caused a rapid development of heart failure. At present, ten years after her first visit to the hospital, her heart is still carrying on fairly well, and this despite small tags of tonsil which I recently observed on careful examination.

As to the treatment of hypertension heart: We must first attempt a lowering of blood pressure because it is the increased work of the heart continued for years without a let-up that causes the heart failure. Hyperpiesia cannot be cured by diet, medication or physical therapy, but the blood pressure can be alleviated in many cases to a moderate degree and the expectancy of hypertension-heart cases can be increased by skillful handling.

Pain and excitement cause greater rises in blood pressure in patients with hypertension than in normals.[8] The reflex arcs, which together with the vasomotor center control, the lumen of the blood-vessels, have a lower threshold and react more intensely in hyperpiesia than normally. It is, therefore, rational to attempt to lower stimuli to the various portions of this reflex arc and if possible to increase the threshold. It is extremely suggestive to observe night blood pressures in hyperpiesia. In many cases the blood pressure will fall nearly to the normal daytime value or even below when the patient is sound asleep and the external stimuli are lessened and the threshold increased thereby for various mechanisms in the reflex. I have found only a very few cases of hyperpiesia in whom the blood pressure would not fall some during sleep.[9,10,11]

Lowering the stimuli is obtained by reducing the mental effort, excitement and worry of these patients. In my observation, most of them are "drivers." They must learn to live at a slower pace, and should find some soothing hobby that will take them away temporarily from their intense interests. They should learn a plan for breaking their routine during the morning and during the afternoon. An hour's sleep after the noon meal does not fit in well with the American plan of work and recreation but it is certainly one of the best means of relaxation and recuperation for these individuals. Golf in the afternoon is all right for these individuals, provided they do not attempt low scores and do not compete in matches. I have been compelled to advise against golf for some patients because they bet on the game and took as much and as intense interest in the winning of the game as they did in the developing and "pushing" of their business. Horseback riding, riding in an automobile for an hour or more with someone else driving provide excellent relaxation. When necessary, a long ocean voyage may be used for relaxation. Many cases of hyperpiesia with blood pressure around 220 to 240 come back from a restful vacation of a month or two with blood pressures down to 180 or 190. Some of the German spas are excellent

for this. The mere assurance of a skillful physician that there is no cause for immediate worry and the establishment of a modified plan of living are often sufficient to cause some drop in blood pressure.

I want to warn against telling a successful and energetic man that he should wind up his affairs and retire altogether from active life. Such advice will certainly not bring down the blood pressure. They must not be relieved of all routine and some relaxing hobby must be substituted. They must not be allowed to feel that they are "has-beens." They must not have too much idle time in which to worry about their condition. Happy the man who can resort to good books at this time. Often the physician will have to prescribe a course of reading just as he has to prescribe certain drug therapy. If the physician can develop a happy disposition in his patient and get his mind occupied in unexciting pursuits, he will have added years and happiness to his patient's life.

Plenty of sleep is of great importance in these cases. About 2 per cent of the students in the Medical School consult me because of high blood pressure. Rarely are these cases of glomerulonephritis. They are usually early stages of hyperpiesia. The blood pressures of these students will often go up 30 to 40 mm. during the weeks before examinations, during which time they work very hard, worry not a little and frequently do not sleep more than four or five hours. Their blood pressures will drop back to their previous though not entirely normal levels when the examinations are over and they get at least eight hours of good sleep. Patients with high blood pressures must have at least eight hours restful night sleep.

When the patient is restless, nervous and cannot lose his "drive," luminal 0.1 gm. (1½ gr.) a day may be tried. Sodium bromid or Sedobrol often help. I also make use of chloral hydrate in these cases and find that 0.2 to 0.3 gm. (3 to 5 gr.) three times a day will often produce an excellent sedative effect. Not infrequently, some drop in blood pressure accompanies this sedative effect. Putting the patient in bed will very frequently bring the blood pressure down very appreciably, sometimes nearly to normal. But as a rule as soon as the patient returns to his routine the blood pressure goes back to where it was previously. Sometimes the rest in bed is advisable before putting the patient on a new routine of living. Under these circumstances, the blood pressure may not go back to the previous high level.

I do not believe that either the low-protein diet, the low-salt diet of Allen or a diet producing an alkaline urine will have much effect upon the level of blood pressure. I have tried them out on standardized cases with long blood-pressure records previous to trying out these diets and have seen no effect in lowering the blood pressure if the patient was previously on a standard régime for some weeks. If the patient is overweight, slow reduction is advisable, but I find

that the effect upon blood pressure is usually slight, unless the reducing is pushed to the point where asthenia develops. Moderation in eating is, of course, to be enjoined.

I believe that tobacco may be used in moderation by many of these patients and I know from experience that taking away tobacco from patients who use it in moderation will usually not reduce the blood pressure. On the other hand, one sometimes finds the blood pressure falling somewhat after complete abstinence in persons who were intemperate in smoking. On the whole, a very moderate use of tobacco probably does no harm and a little smoke often has a relaxing and sedative effect that is not undesirable. A pipe often relaxes more than a cigar, and less tobacco will be consumed in a small pipe than in one ordinary cigar. Where angina pectoris or extrasystoles or palpitation are present, it is sometimes of benefit to stop smoking entirely.

Tea and coffee may be used in moderate quantities. Intemperance in tea or coffee may be harmful but in many patients a moderate quantity will be found to produce no harm.

The physical activities of the patient must be reduced to a very moderate amount in my opinion. The heart which sustains a pressure of 240 systolic and 120 diastolic is performing approximately twice as much work every beat as the heart which is putting out the same stroke volume at a pressure of 120 systolic and 80 diastolic[12]. As this goes on every hour of the day and may go down somewhat only for a few hours at night, it can be easily calculated that these hearts are doing more work every day than the hearts of college athletes engaged in strenuous sports.[13] When individuals with these high blood pressures engage in strenuous physical exertion the amount of work performed by their hearts is as much greater than the amount of work performed by the heart of an individual with normal blood pressure and engaged in the same physical exertion as the systolic pressure of the one is greater than that of the other. Unquestionably some so-called athletes' hearts were the hearts of individuals who engaged in athletics and had high blood pressures. It has been my observation that men who do hard physical work do not stand high blood pressures as well as those who lead sedentary lives. The men who do hard labor succumb to heart failure earlier.

The nitrites I only use in emergencies. Bloodletting (400 to 600 cc.) will reduce the blood pressure temporarily but it is back in twenty-four to forty-eight hours as a rule. It can be used in pseudo-uremic attacks and emergencies, and there are patients who feel much better for a month or more after a venesection.

Despite my academic attitude on the effect of chronic foci of infection on hypertension heart, I advise strongly a careful search for and elimination of all foci as far as possible. Every source from which Streptococcus viridans can invade the body should be eliminated, if possible. Infection may at any time arise from these sources to produce bronchopneumonias, lobar pneumonias, or rheu-

matic infection, or to cause thrombi in inactive auricles, or upper respiratory infections; all of which may be of serious consequence to the patient. The physician must always do everything possible to help his patients, even if the scientific basis of the treatment is not established, provided the treatment can do no harm; he cannot wait for the clearing up of scientific questions before beginning treatment of his patients.

But despite everything, sooner or later, the heart will fail severely and we must then treat the heart failure like any other heart failure. Where there is auricular fibrillation, digitalis often works wonders. I am convinced that digitalis also helps materially when there is no auricular fibrillation though not so spectacularly. Digitalis rarely increases the blood pressure excepting now and then in a very few badly decompensated cases through bringing about a disappearance of the heart failure. Under these circumstances, the increased blood pressure with compensation is preferable to a lower blood pressure with decompensation. For relieving stubborn edema I try theocin first: 0.1 gm. (1½ gr.) three times a day, on the first day, 0.1 gm. five times a day on the second, and if there is no diuresis 0.1 gm. six to eight times a day on the third. This dose can be given for a few days, after which it will usually be necessary to stop because of nausea, vomiting and headache. It is best given after meals. Diuretin, 3 to 5 gm. a day, will often bring about a diuresis but is not nearly as efficient as theocin. Sometimes when theocin fails, ammonium chlorid and novasurol will still produce a diuresis. We usually give 8 gm. of ammonium chlorid or nitrate on the day preceding the injection of novasurol and keep up this dose of ammonium chlorid until the edema has disappeared or the patient will not tolerate it any longer. On the second day, we give 0.5 cc. of novasurol intravenously. If this is ineffective we give 1 cc. on the fourth day and if necessary 1.5 cc. on the sixth day. Then 1 to 1.5 cc. at two-to three-day intervals until the edema disappears. Where the ammonium chlorid is not tolerated we give the novasurol without it.

As there is some degree of coronary sclerosis associated sooner or later with most cases of hypertension heart, I believe that euphyllin is indicated because of its property of dilating the coronary arteries.[14] It is also a mild diuretic. We give 0.1 gm. five times a day. If diuresis is also desired, 0.2 gm. five times a day. I know of no contraindications for euphyllin and I have used it for long periods in the same patient daily and my impression is that it has often been of real benefit. Nitroglycerin and nitrites may also be used in these cases to relieve attacks of angina and to dilate the coronaries.

But the best therapeutic measure we have for these fatigued hearts is rest. I believe in prolonging the bedrest for months, and long after compensation seems assured. And the results obtained therewith speak eloquently for this prolonged bedrest. It is neces-

sary to give sedatives when one sees these patients first, as they must have sleep and they must lie quietly relaxed. There is nothing better than morphin but it is not always necessary. Two tablets of allonal will often produce a good night's rest. Or a combination of chloral hydrate, 0.5 gm. (7½ gr.), and codein, 0.03 gm. (½ gr.), or chloral hydrate, 0.5 gm. (7½ gr.), and luminal, 0.1 gm. (1½ gr.), will be sufficient for a good night's sleep. There are an infinite number of combinations of soporific drugs that will work well in many of these cases. To keep the patient sleepy and quiet during the first few days of severe decompensation, 1½ to 2 gr. of luminal per day or 15 gr. of chloral hydrate divided in three doses during the day, if the blood pressure is over 180 systolic, will work excellently in many cases. Where there is a cardiac psychosis, scopolamin hydrobromid 0.0003 to 0.0004 gm. ($\frac{1}{200}$ to $\frac{1}{150}$ gr.), two or three times a day with morphin will often help. If there is depression of the respiratory center from the scopolamin, add 0.025 ephedrin with each dose of morphin and scopolamin.

When marked cyanosis develops and the venous pressure goes above 20 cm. of water, a venesection of 500 to 600 cc. will often bring about great relief of dyspnea and cyanosis and ward off, temporarily at least, death from right heart-failure. The venous pressure can be determined by measuring the height above the chest in recumbency, at which the veins on the back of the hand collapse. (Middleton.)

Those patients who can live without work or exertion after serious decompensation, as a rule have the longest periods of freedom before the next attack of decompensation comes. But sooner or later, it will come. In a few, an attack of coronary thrombosis will end the scene. In most of them a severe attack of heart failure will be prolonged for a few weeks or months with ultimate death in severe decompensation, or a bronchopneumonia will intervene to hasten death.

It is remarkable how long some of these patients will last after the first attack of severe decompensation, if skillfully handled. Three and even four years is not very uncommon even in those seen in the University Hospital and Dispensary. Usually the expectancy after the first attack of severe heart failure is less than this, not more than from one to two years. I have one good series of hospital and dispensary records of a patient who lived seven years after a first attack of severe decompensation.

Sometimes surgeons hesitate to perform desirable operations upon patients with hypertension and some degree of heart failure. My experience would indicate that in high blood pressure with only moderate symptoms of dyspnea on exertion the risk of operation is no greater than in other patients of the same age. These patients may also be operated upon with very little increased risk from the operation if they have had more severe heart failure but

have been well compensated through medical management. When auricular fibrillation is present, the risk from operation is greater, but even with auricular fibrillation the risk is not great, provided there is good compensation.

Appendix. Any calculation of the number of deaths consequent upon hyperpiesia derived from the mortality statistics of the registration area of the United States has inherent in it considerable error and uncertainty. The calculations which I have derived from different sourses of information vary from one another by about 10 to 15 per cent. But it is possible to get what must be a very fair approximation and the order of magnitude of this figure from a study of the mortality tables.

The mortality statistics for 1924 give 78,000 deaths from cerebral hemorrhage in persons fifty years of age or over. It is very conservative to reckon on 47,000, or 60 per cent of these, as associated with hypertension. The data collected by Dr. E. T. Bell from the autopsy material of the University Pathological Department indicates that a much larger percentage of all cases of cerebral hemorrhage and encephelomalacia are associated with high blood pressure, but we have adopted 60 per cent in order to underestimate rather than overestimate the number of cases of hyperpiesia. Chronic nephritis is credited with 65,000 deaths in persons of this age category. True chronic glomerulonephritis is a fairly rare disease at this period of life, as every pathologist conversant with the modern classification of nephropathies knows. Romberg, in his *Lehrbuch der Krankheiten des Herzens*, fourth edition, page 263, states that during a certain period in his clinic in Munich there were 656 cases of arteriolar sclerotic kidney (hyperpiesia) and only 58 cases of chronic glomerulonephritis with high blood pressure. We may assume most of the cases classified in the mortality statistics as chronic nephritis had high blood pressure. I have assumed that more than 32,000, or 50 per cent, of all the cases of so-called chronic nephritis were really renal arteriosclerosis and therefore belonged with the hyperpiesia cases. There were 140,000 deaths from heart failure in persons over fifty years of age. In the Minneapolis General Hospital and the University Hospital, and in the Pathological Department of this University, about 70 per cent of all heart failure not due to chronic valve defect or lues, are associated with hypertension. Making use of Wyckoff's and Lingg's figures on the etiology of organic heart disease (*Am. Heart J.*, 1926, **1**, 446) at various decades, I calculate that at least 92,000 must have belonged to the group of heart failures due to primary disease in the heart muscle or coronary arteries. My own statistics show that at least 70 per cent of these cases are associated with high blood pressure and I, therefore, calculate at least 64,000 cases of hypertension heart in persons dying fifty years of age or older in 1924, using the above data. The total number of deaths associated with hyperpiesia is 143,000 as calculated from the above figures.

We can calculate the number of cases of hypertension-heart death from other data. Fifty per cent of all the cases of organic heart disease older than forty-five years visiting the Cardiac Division of the University Dispensary have high blood pressure. If we use this figure, we calculate 70,000 cases of hypertension heart in persons fifty years of age or older from the 1924 mortality statistics. There are a large number of cases of hypertension coming to the Cardiac Dispensary and not classified as hypertension heart because there are no symptoms or signs of heart failure present. These cases are two-thirds as many as those classified as hypertension heart. Many of these will die of heart failure ultimately and we, therefore, are inclined to believe on the basis of this data that there are more than 70,000 cases of hypertension heart deaths. I believe that a death rate of 140,000 for hyperpiesia for the year 1924 and in persons over fifty years of age is very conservatively reckoned. This is 23 per cent of all deaths in persons fifty years of age and older.

Summary. Approximately 140,000 persons in the United States die each year from the consequences of high blood pressure. Approximately one-half of these deaths are due to cardiac failure consequent upon high blood pressure. The hypertension heart is frequently incorrectly diagnosed as myocarditis or mitral insufficiency. The diagnosis "arteriosclerotic heart" is also inappropriate unless coronary arteriosclerosis is present.

The hypertension heart is characterized by an increase in weight, largely due to hypertrophy of the muscle fibers of the left ventricle. In addition, there is a characteristic dilatation of the left ventricle in later stages.

The symptoms of heart failure develop about twelve to fifteen years after the onset of the hypertension, if there is only a very moderate degree of coronary arteriosclerosis present and if no other complication has developed in the meantime. These symptoms of heart failure in hypertension heart do not differ essentially from the symptoms found in heart failure due to other types of cardiac pathology. Pulsus alternans is more frequently found in hypertension hearts than in any other type of heart disease.

The blood pressure may remain high, even up to within twenty-four hours of death in heart failure. In other cases, the blood pressure may fall after the onset of severe heart failure, especially if auricular fibrillation is present or if there is a considerable degree of coronary sclerosis.

The treatment should be directed toward lowering the blood pressure insofar as this is possible and toward reducing the physical activities of the patient, thus reducing the work of the exhausted heart muscle. Digitalis, diuretics and sedatives have the same indications as in other forms of heart disease with failure. Long continued bedrest is probably the most effective measure in handling this type of heart failure. Venesection helps in emergencies where the venous pressure has risen above 20 cm. of water.

The operative risk in cases of hypertension heart, well compensated at the time of operation, is very little greater than in normal cases.

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THE TEN-YEAR DIABETIC.*

What He Is. What He Should Be. How to Make Him So.

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1. What He Is: Theoretically, he does not exist, because the average duration of life of the diabetic has not yet reached eight years, but practically he is very much alive and he and his confrères present the chief diabetic problem of today in your practice and in mine. In talking about him, I feel a little like the minister who turns his barrel of sermons upside down because he formed the topic for a paper fifteen years ago.[1]

Age at Onset. At present this ten-year diabetic is a diabetic whose disease began when he was neither young nor old, not before fifteen years of age or after sixty-eight years of age. Last year I could find record of only 13 cases of diabetes in children in the

* Read before the Interstate Postgraduate Medical Association of America, Kansas City, Tuesday, October 18, 1927.

United States, living or dead, who had survived their disease a decade. At sixty-eight years the expectation of life of us all begins to fall below ten years. How many instances of these ten-year diabetics in childhood there are today I cannot say, but in my own series the number has risen to 10. A diabetic whose disease begins at seventy years has one chance in 500 of becoming a ten-year diabetic and of my ten-year diabetics constitutes but 0.3 per cent.

Most frequently the ten-year diabetic is one whose disease begins in the fifth decade of life, next in the sixth, then in the fourth and from these decades falls off rapidly in both directions. It is of interest that their figures for age at onset hold for the series prior to 1912 as well as for the entire series.

Sex. The distribution of ten-year diabetics by sex is essentially the same as for all the diabetics. Thus 624, or 54 per cent, in my series are males.

Frequency. In 1912 there were 31 of my true diabetics who had lived ten or more years, but today there are, living or dead, 1161, or 22 per cent of the total cases. Up to 1912 only 7 per cent of the patients had lived ten years, but upon a restudy of this group after the lapse of these fifteen years, I find to my surprise that eventually 35 per cent reached that goal. We built better than we knew in the Naunyn era.

For comparison, take the 1329 cases of true diabetes this last year. Of this number, 20 per cent had already lived ten years, which makes it perfectly evident that a resurvey of all diabetic patients fifteen years hence will then show that it is the exception to die of diabetes before the course of the disease has run a decade. Indeed, this duration has been nearly attained already by 152 fatal cases with onset between forty and fifty years in the Banting era, because it was nine and four-fifths years. There is good reason to predict that every diabetic will be a ten-year diabetic, not by and by, but soon. Further, in any discussion of the number of ten-year diabetics it is only fair to point out that we have had insulin but five years.

Tenth Diabetic Anniversaries. The celebration of tenth diabetic anniversaries is worth while. They are cheering to the patient and his family as well as to the doctor. They are helpful because they challenge one's skill in treatment; they promote thought to determine why one case attains and another fails to reach the mark. Eleanor, whose diabetes began when she was a child, will have her tenth diabetic anniversary next week and to the reception in her honor invitations will go out to 230 other diabetic children. Why do you not have a tenth diabetic anniversary party too, and if not for a child then for your youngest adult? It promotes morale.

Every diabetic I see whose onset is above the age of sixty-seven years generally lowers the average duration of all my cases. Therefore, I welcome the young diabetic and the younger the better.

This last year the mortality for the 1205 cases I saw and traced was 3.5 per cent, but for the 235 children, of whom I know the condition of all but 2, was 1.3 per cent. When I hear the slurring remarks about the success of modern diabetic treatment, I feel as annoyed as the blind man of old under similar circumstances after his sight was restored and like adapting his words to the present situation. But one thing I know, whereas my diabetic children died, now they live. The duration of life of the average diabetic child in my group has advanced one year these last twelve months.

Causes of Death. You can hazard a good guess of what a diabetic is if you know of what he dies. This was not true in the Naunyn era ending in 1914, when coma caused 61 per cent of all diabetic deaths or even in the Banting era up to July 1, 1926, when the percentage of deaths from coma was reduced to 20, but it is true of the 42 deaths which occurred among the patients I saw last year, because in the 91 per cent thus far traced coma has not been reported in a single instance.

In contrast to the abolition of coma is the steady increase of cardiovascular and renal deaths on the death certificate. Hitherto a diabetic in his first year meant an arteriosclerotic in his tenth year. Thus in the Naunyn era the percentage was 15 per cent, but in the Banting era up to July, 1926, it was 47 per cent. These figures are for all diabetics, but for those diabetics with a duration of ten to ninteen years inclusive it rose to 54 per cent.

Approximately one-half of the deaths in this last year's series of 42 deaths were from cardiovascular and renal conditions, and save for cancer, 14.7 per cent, the other causes of death were scattering and had little connection with diabetes. Only 1 case of the 42 died of tuberculosis.

Arteriosclerosis, therefore, has replaced coma as a cause of death in diabetes. So common is arteriosclerosis a factor in diabetes today that Dr. Morrison was able to demonstrate its presence in 86 per cent of cases of ten years' or more duration. Studied by Roentgen ray our pathologists found it in every necropsy upon a diabetic, young or old, of five years' duration.

The ten-year diabetic is apt to be a gall-stone diabetic. Statistics upon the frequency of gall stones in diabetes are of comparatively little value unless based upon necropsies. At the Deaconess Hospital in our series of autopsies upon diabetics above the age of twenty-five years 31 per cent show gall stones. This is irrespective of the duration of the diabetes.

The Average Age of Diabetics at Death. The age at death of 42 fatal cases in this year's group is of interest because of comparison with previous figures. Thus of the 339 cases in the Naunyn period, the average age at death was forty-four and four-fifths years; in the Banting epoch, ending July 1, 1926, for 607 fatal cases it was fifty-four and one-fifth years; for the 60 cases in the twelve months

ending July 1, 1926, it was fifty-nine years; but for these last twelve months the average age was sixty and nine-tenths years. Therefore, the average diabetic whom I see need not expect death until he is past the age of sixty-one years, or three years later than the average citizen of Massachusetts. The statement for this series is also true that for the thirteen years since 1914 the average age of my diabetics at death has advanced sixteen years. This leads to a query. Doctor, do you think you can live to be as old as your average diabetic when he dies? The average of the 1200 cases of Dr. Rabinowitch, he writes me, is forty-seven years. He must, therefore, keep them alive fifteen more years. He has youth at his elbow and I believe can do it.

TABLE I.—TYPES OF ONSET OF DIABETES (100 CASES).

		Cases.	Per cent.
Indefinite	2 mos. or more.	81	81
Gradual	1 to 8 wks.	15	15
Rapid	1 to 7 days	3	3
Sudden	24 hours	1	1

TABLE II.—AGE AT ONSET BY DECADES OF 162 DIABETICS WHOSE DURATION IS TEN YEARS OR MORE (1898 TO JUNE, 1912).

Decades, onset.	Cases.	Per cent.
0 to 9	1	0.6
10 to 19	4	2.5
20 to 29	11	6.8
30 to 39	24	14.8
40 to 49	57	35.1
50 to 59	50	30.8
60 to 69	15	9.3
70	0	0

TABLE III.—AGE AT ONSET BY DECADES OF ALL DIABETICS WHOSE DURATION IS TEN YEARS OR MORE (1898 TO JULY, 1927).

Decades, onset.	Cases.	Per cent.
0 to 9	4	0.3
10 to 19	18	1.6
20 to 29	68	5.9
30 to 39	199	17.1
40 to 49	454	39.1
50 to 59	324	27.9
60 to 69	90	7.7
70	4	0.3

Diabetes Milder the Longer it Lasts. Do you know of a severe diabetic of ten or more years' duration? It is true they may exist, but they are pretty well disguised with the help of insulin. Whereas formerly we were expecting diabetics to get worse, now we must be on the watch for them to get better. You may say, of course, there are no severe ten-year diabetics, because they have already died. To which I reply—How many a ten-year diabetic appeared severe

at the start to the physician who first saw him! As the duration of diabetes lengthens, its symptoms lessen and fade away.

2. What He Should Be: The ten-year diabetic if over thirty-five years of age should be of normal weight. There is no need to dilate on this statement. The ten-year diabetic should be the finest product of the periodic health examination. The handicap of the diabetic must be offset by the prophylactic treatment of the doctors. No group of individuals is more constantly under a doctor's care and consequently they constitute what one may call the "doctor's diabetic trust." Woe to us physicians if we do not administer that trust in a way to give large returns in dividends of health to our patients.

If, by chance, a doctor is a diabetic he should become a diabetic specialist when he has passed ten years of this disease, or possibly even earlier if he has reached the age of sixty years. I have known more than one doctor whose diabetes was his salvation, just as tuberculosis has been the salvation of other doctors. The Pennsylvania doctor I have in mind developed diabetes at about sixty years of age, retired from active general practice, took up special work on diabetes, and because of the great respect in which he was held in his community within a single year treated 100 cases of diabetes. Cheer up, Doctor Diabetic, there are bright days in store for you if you will only play the game and be a ten-year diabetic. No ordinary diabetic should become a diabetic specialist. Indeed, no one should be a diabetic specialist, whether he has the disease or not, at least until after the age of sixty years, although in his earlier years he may have a bent toward diabetes, because he needs the training of a general practice first, last and all the time.

The ten-year diabetic should have less arteriosclerosis. This will be taken up under its prevention.

3. How To Make Him So: **The Early Diagnosis of Diabetes.** If the diabetic is to be in good condition at the end of ten years his disease must be detected early. Early treatment keeps him mild. Yet my records show that in 81 per cent of 100 recent cases the patient had no idea just when his disease began and could not date its onset to any given two months' period. To discover diabetes early one must seek for it where it is overwhelmingly common, and this is in the obese and between the ages of forty-five and fifty-five years, and especially in women. Therefore, the fat public between these ages should be penalized and undergo one examination of the urine for sugar each month until their weight comes to within at least 10 per cent of normal. Any physician who wishes his patients to know he is alert should either do this for them or teach them the Benedict test. Here is where the individual of normal weight scores, because for him an examination on his birthday is relatively safe until he is forty and after that upon New Years' and the Fourth of July.

Children's Diabetic Camps. Diabetic children should be taught to live like other children and have their joys. The parents of those diabetic children who went to a girl's diabetic camp this summer told me that never before had their children spent such happy weeks or looked so well. This is an idea worth promulgating. Every large hospital or clinic throughout the country, every city, should begin to plan for a children's diabetic camp next summer. Commence on a small scale and watch the camp grow. The camp I know of was managed by a nurse and there were five children. They hiked, swam, played, published a paper and no one said to them "you have diabetes, you are different." I consider the beginning of children's diabetic camps the most notable concrete advance in the practical management of diabetic children I have known this last year. There have been camps for the healthy, camps for the child with tuberculosis, but never so far as I am aware a summer outing camp for the diabetic child. Almost anybody who has a cent and has known a diabetic child will give you money toward it. Last year the camp was for the well-to-do, but this coming year a camp will be arranged for the child in moderate circumstances and the poor child. Already the mother of one of the girls has given me her home by the seashore for it, because her daughter profited so much from the experience this year, and the Rev. Mr. ——. has promised to take any diabetic boys I will send him. Several Boston friends of mine have inaugurated its financial support.

The Prevention of Arteriosclerosis. The ten-year diabetic has arteriosclerosis; should not have arteriosclerosis; but how can he avoid it? I do not believe he has it because he is preordained and predestined to have it on account of his diabetes, but I believe he has it largely because we doctors give it to him. Of course, I am only referring to premature arteriosclerosis, to the arteriosclerosis which comes on in youth and to that which is in excess of the quantum which is due his age.

Carbohydrate and Fat. All agree that extreme restriction of carbohydrate causes acidosis, but is it not probable that immoderate feeding of fat leads to arteriosclerosis? Do the fat or the thin with diabetes develop arteriosclerosis early? Is it the diabetic with a low-carbohydrate and high-fat diet who develops it or the diabetic with a high-carbohydrate and a low-fat diet? I believe it is the former. I believe the reason why we see premature arteriosclerosis in young diabetics is, because formerly we were only able to keep them alive with a low-carbohydrate and high-fat diet. Insulin has brought better days. Not one of my diabetics now takes less than 50 gm. of carbohydrate, and I am trying to raise their diets gradually up to 100 gm. of carbohydrate. I do not go as far as Geyelin, still less as far as Sansum, in giving very much larger quantities, but I think each one of us should closely follow their work and watch for the publication of their statistics. The diabetic whose disease is

diagnosed early can maintain a diet amounting to carbohydrate 100 gm. or more, if he is not overfed with fat, and temporarily it is desirable to keep his fat low and near the normal level to enable him to regain his tolerance. Never overfeed a diabetic and least of all with fat. This then is my first rule to avoid arteriosclerosis in my future ten-year diabetics.

Protein. The protein may be a factor and it may be taken for granted that it should be limited to a moderate amount, not far from 1 gm. per kilogram body weight, to less than 1 gm. in the old, to more than 1 gm. in the young.

Hyperglycemia. Hyperglycemia does not seem to me to be a cause of arteriosclerosis. From what information I have been able to gather in the literature and upon inquiry, depancreatized dogs do not develop arteriosclerosis prematurely. Indeed, hyperglycemia may be a conservative phenomenon. At any rate, do not lower the blood sugar suddenly in an old patient. Remember the patient with high blood pressure tends to acquire a high percentage of sugar in his blood. Perhaps his heart with its thickened coronary arteries requires it.

Cholesterol, Eggs and Arteriosclerosis. I wonder if you will agree with me that the cholesterol deposits of atheromatosis are premonitions of a later calcification. If you do, do you think it is desirable to feed diabetics more cholesterol than the normal individual? Blaisdell and Chandler[2] show by their experiments with animals that the percentage of cholesterol rises in the blood and is deposited in the tissues when an excess of cholesterol is fed. The animals retain it rather than excrete it. Do you think your diabetics are any different? Letulla, Labbé and others directed attention to this years ago. Diabetics generally have an excess of fat in their food, in their body, and specifically an excess of cholesterol in their blood. We know they have an excess of cholesterol in their arteries, why should we force more upon them and yet that is what you and I have been doing for years. Why do we give them one, two, three, four or even more doses of 0.38 gm. of cholesterol a day? To your other patients you do not give more than one or at the most two eggs daily. I believe that until it is proved that the cholesterol in the blood of diabetics is low, it is wise to give few rather than many eggs, and when a diabetic shows signs of arteriosclerosis he should be restricted to one egg, but that we should not go any further in the restriction of eggs until we have proof that it will do good.

Professor Bloor tells me that an egg contains 0.38 gm. of cholesterol, and a man of 75 kg. would contain perhaps 50 gm. of cholesterol or 0.7 gm. per kilogram of body weight. Apart from eggs, the quantity of cholesterol in foods is comparatively low; that in vegetables is so low as to be entirely negligible; that in bacon, while higher, is also too low to be considered important. Olive oil sometimes contains as high as 1 per cent cholesterol and corn oil (Ander-

son) about 2 per cent. The two latter are worth noting, because of their use as salad oils. Cholesterol is essential and is to be found in practically every cell of the body. Evidently we need a good deal of it. Do we manufacture it or eat it only ready made? Can we destroy it or merely excrete it and can we hasten its excretion when it is present in excess?

The egg question should be investigated. Eggs produce growth in infancy. Are they desirable for the old? Have centenarians used many eggs? What is the cholesterol content of the blood of groups of individuals who have had the egg habit, of races who do or do not eat eggs? Are eggs fed to our prisoners, to our insane, and with what cholesterol and arteriosclerotic results? Learn the habits of your arteriosclerotic friends. After fifty, are you planning to eat two doses of cholesterol for breakfast, or one egg and bacon? We do not know about eggs and arteriosclerosis. We all want to know and we can and should find out soon.

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THE BORDER ZONE BETWEEN THE HYPERPLASTIC AND NEOPLASTIC PROCESSES OF CUTANEOUS EPITHELIUM.

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These border zones have been bothersome to the pathologist for a long time; one needs but to mention the lymphatic hyperplasias of some chronic inflammations in the same breath with such conditions as lymphosarcoma and Hodgkin's disease. Similarly, in breast cancer, McFarland[1] has done much to clear away one item, abnormal involution, from the processes which litter another twilight zone. The skin, too, has its border zone; it is the purpose of this communication to chart the different cutaneous changes which lie in this zone and to indicate the affinities of each with hyperplasia on the one hand and neoplasia on the other. It will be recognized at once that the skin, a unique organ in many ways, is outstanding because its lesions are so accessible to study. The skin has been open to the direct observation of generation upon generation of physicians, and as a result it has been possible to arrange symptom complexes as in no other organ. In connection with neoplasia, it has permitted as ideal a comparison and check-up between the histo-

pathology and the clinical phases as could be imagined; it led long ago to the recognition of the differences in prognosis, for instance, between squamous-cell and basal-cell cancer. In this paper I would stress the importance of such factors as metastasis, deep permeation and destruction of tissue in the appraisal of malignancy, and hope to demonstrate that in the skin the border zone between hyperplasia and neoplasia is exceptionally broad, and that there are several forms of epithelial hyperplasia which must be assigned to it instead of being placed in the malignant territory to which the classic criteria of general histopathology would relegate them.

The propensities of the different portions of cutaneous epithelium for undergoing hyperplasia will be dealt with in order in the suc-

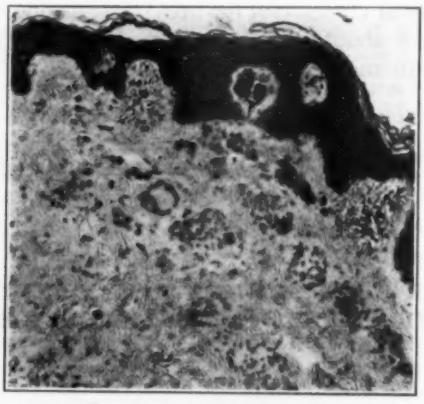

FIG. 1.—Simple cellular nevus. This is the classical picture; there is never any doubt here as between nevus and cancer.

ceeding paragraphs. It will be noted among other things that, whereas the histological criteria would urge them toward the territory of malignancy, the clinical criteria (metastasis, invasion, and so forth) consistently compel a shift in the opposite direction.

Pigmented Nevi. Although the epiderm often participates, the cells in the corium are the important features of the nevus to which I wish to call attention. These cells of a typical nevus occur in the papillæ and subpapillary parts as globular cells with a fairly large nucleus, the cells usually lying in clusters, sometimes associated with giant cells. While this is the type picture and, once familiarized, never gives trouble in diagnosis, there are all sorts of variations in both directions. Sometimes cells are so scarce as to delay diagnosis. At other times the cells are large, present in great numbers and extend far downward into the corium; they may then imitate carcinoma. Further details cannot be entered into in this paper, but one or two illustrations of the close resemblance between pigmentary nevi and carcinoma may be submitted. In Fig. 2, for

FIG. 2.—Pigmented papillomatous nevus, showing quasipermeation of the corium.

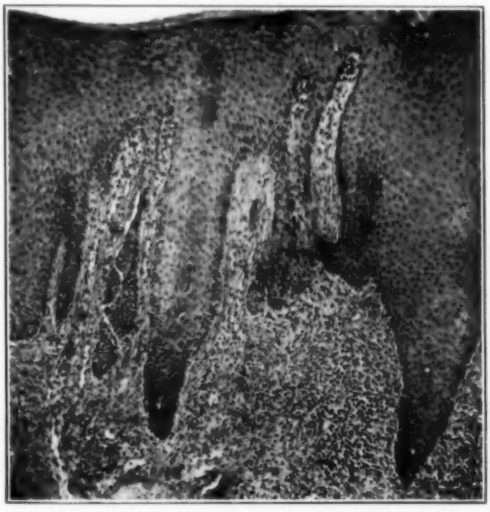

FIG. 3.—Acanthosis, severe grade, occurring at margin of cutaneous ulcer. No resemblance to cancer; compare with the more irregular expressions of acanthosis in succeeding figures.

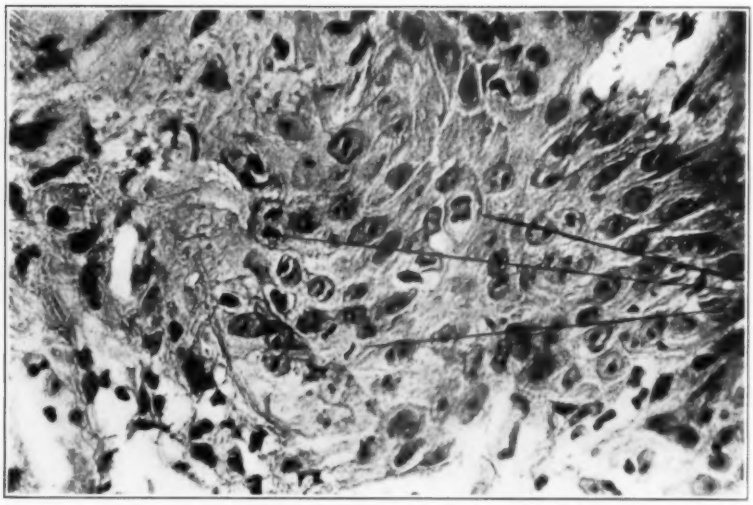

FIG. 4.—Pseudoepitheliomatous hyperplasia. Indefiniteness of basement membrane due to edema and round-cell infiltration. Three mitotic figures at *M*.

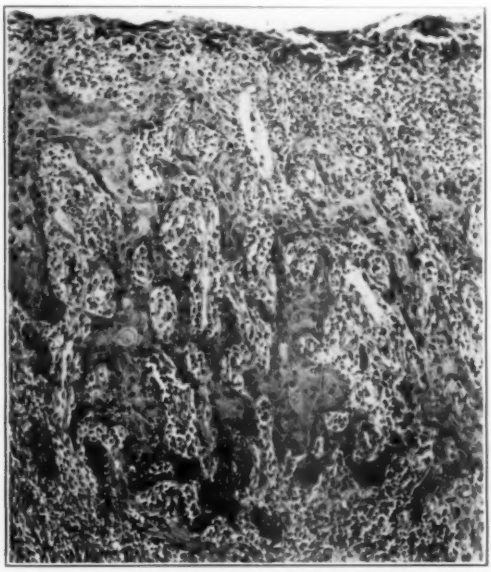

FIG. 5.—Pseudoepitheliomatous hyperplasia of extreme grade. Histologically indistinguishable from squamous-cell carcinoma. Lesion healed under local medication.

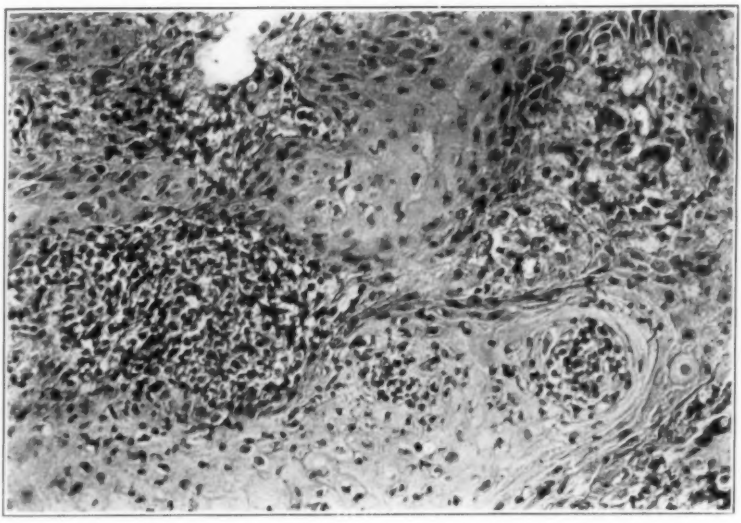

FIG. 6.—Blastomycosis. Hyperplasia of prickle cells taking the form of cancer. Two miliary abscesses (one larger and one smaller) are included in this illustration and are valuable differential diagnostic factors.

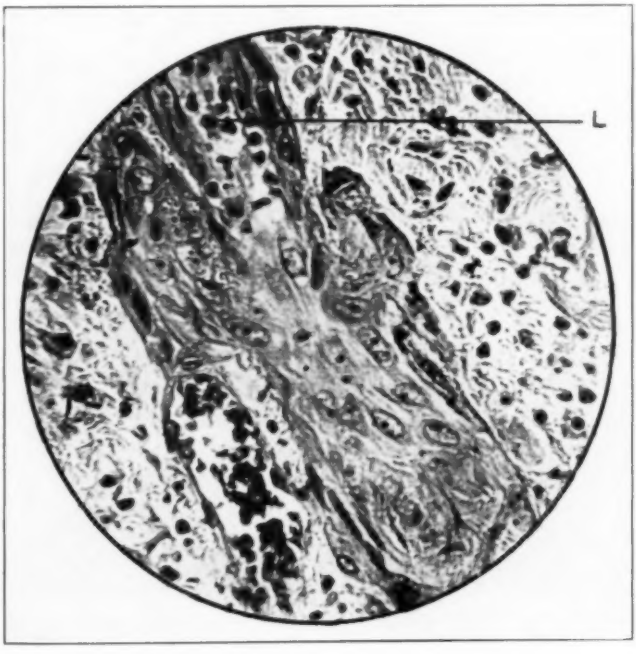

FIG. 7.—Hyperplasia and metaplasia of sweat-duct epithelium in erysipelas. Leukocytes present in the lumen at L.

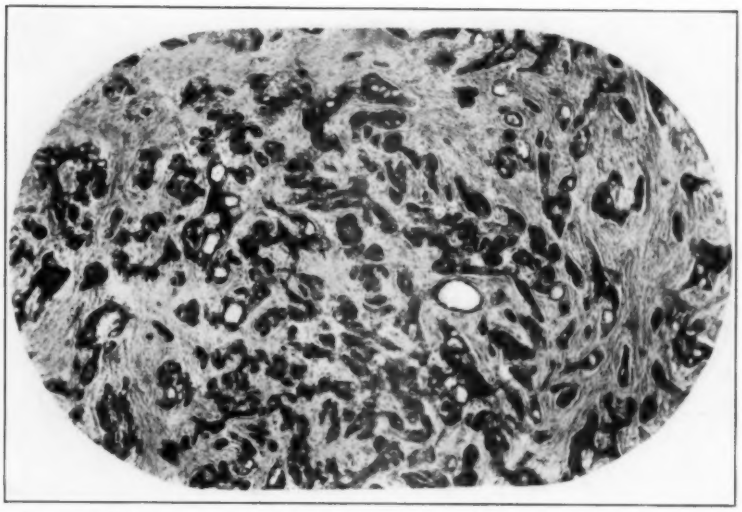

FIG. 8.—Syringoma. A harmless, although disfiguring, affection of the face and chest which has been known also as benign cystic epithelioma and which has the histology of cancer.

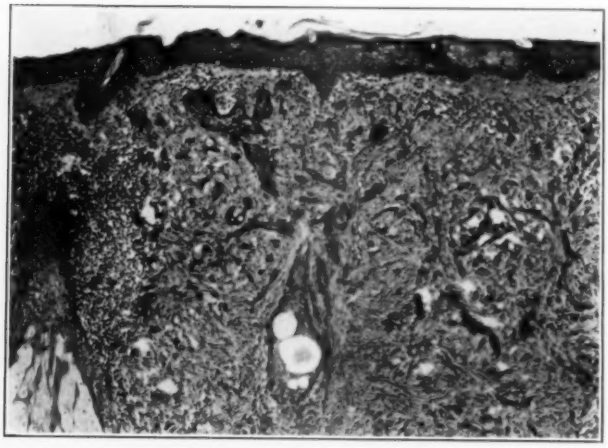

FIG. 9.—Trichoepithelioma. Origin of lesion in hair follicle. Considerations same as in syringoma; harmless clinically, but histologically malignant.

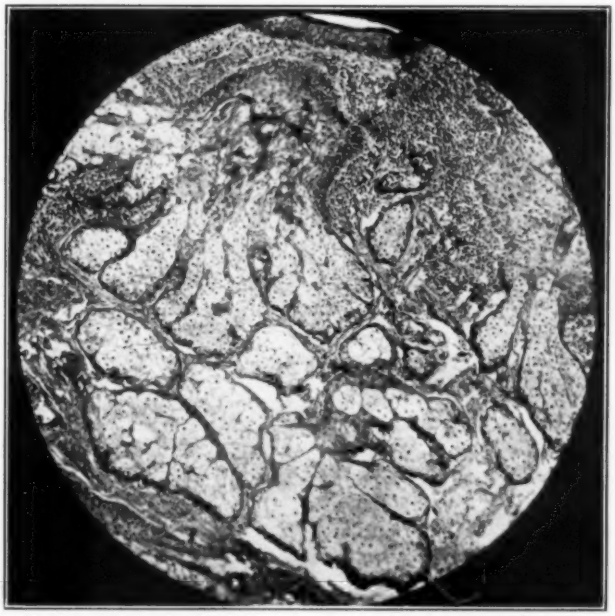

FIG. 10.—Hyperplastic sebaceous glands in skin of face. Demodex folliculorum was present in large numbers.

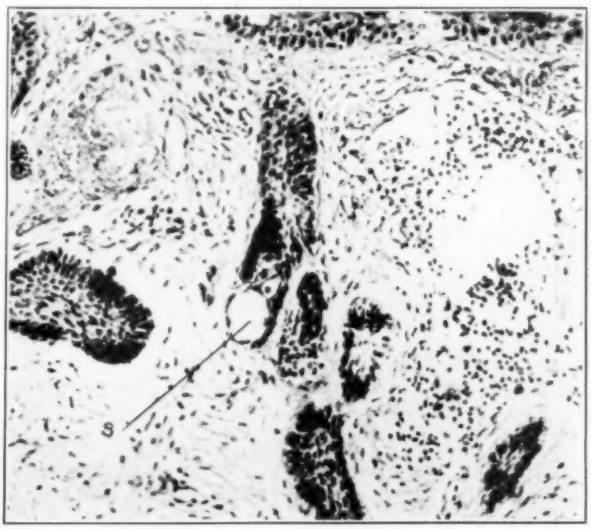

FIG. 11.—Basal-cell cancer extending from pilosebaceous apparatus. There is a small cluster of sebaceous cells at *S* which serves in identification.

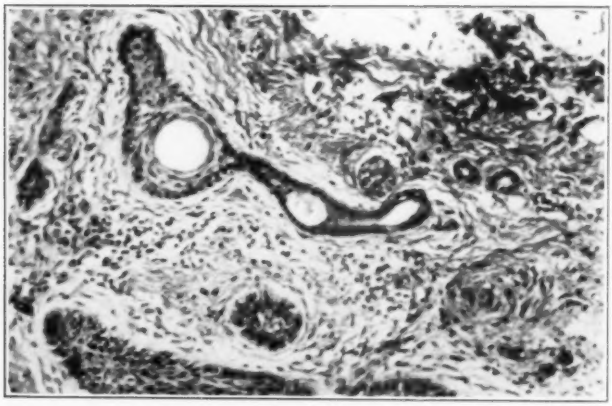

FIG. 12.—Sweat ducts in same section as Fig. 11. Hyperplastic changes in their walls of the same order as the basal-cell cancer elsewhere. Clinically this was the extremely benign form known as "Pagetoid carcinoma."

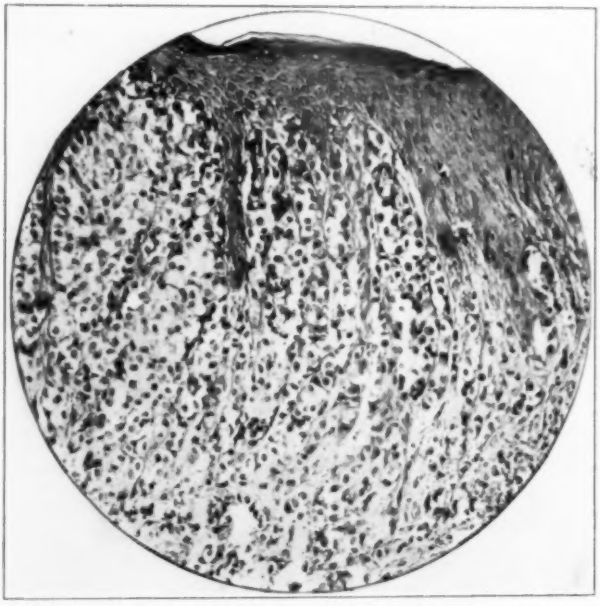

FIG. 13.—Nevocarcinoma. Origin of cells from epiderm traceable at right-hand side of illustration. "Resting" nevi do not show perpendicular tracts of cells like this one.

instance, there appears to be true neoplastic permeation of the corium, yet this lesion presented no other features of neoplasia and came from a necropsy subject dying of nephritis. Furthermore, the same picture is frequently repeated in pigmented and papillomatous nevi secured by biopsy from cases in which there has been no undue activity for years, nor other evidences of malignancy. Here is a lesion, then, which teaches two lessons: (1) That from simply a knowledge of general pathologic principles the real nature of the affection could scarcely have been made out; only from having seen previous sections of nevi could the observer make a diagnosis. (2) That the histologic picture in numerous nevi may be that of carcinoma, yet the clinical circumstances conclusively prove that, biologically, the condition is not cancer. If these lesions had occurred in internal organs it is doubtful, indeed, if their nonmalignant nature would ever have been determined; but located as they were upon the skin, and observed from month to month and year to year, and coming to microscopic examination (as was the case in the sections here illustrated) after the death of the individual from another disease, their real nature has been finally established.

The Epiderm. The epiderm is the portion of cutaneous epithelium which is most commonly found hyperplastic. In a great variety of inflammatory processes, ranging through eczema, psoriasis, syphilis and blastomycosis, the cells may be found hyperplastic to such an extent that even epitheliomatous invasion may be imitated. In the milder expressions of hyperplasia the interpapillary pegs become but slightly elongated and maintain a rather regular contour; in the severer grades, however, they become irregular, both as to size and shape and extension downward into the corium. This is designated acanthosis, and may be dismissed with the statement that for the skin it is the stock expression of reaction against irritants of many categories—radiation, chemicals, endogenous products and specific microörganisms.

At this place special mention should be made of the pseudo-epitheliomatous hyperplasia which may occur at the margins of old ulcers; it is really a variety of acanthosis. In most cases careful study will satisfy the pathologist that such a hyperplasia is not a malignant one, but in others he will remain in doubt, and occasionally the appearances may be quite those of squamous-cell carcinoma. Indeed, every one of the criteria commonly employed in the histologic diagnosis of cancer may be included in the complex, and but one feature (a clinical one) remain to finally guide the pathologist; namely, the fact that the hyperplasia occurred at the margin of an ulcer and that the clinical follow-up has demonstrated that hyperplasias which are malignant histologically may be benign clinically. That is, that treatment other than that of carcinoma will be followed by the healing of the ulcer and none of the further progress of cancer.[2] I am confident that many unnecessary surgical operations have been

performed upon indolent ulcers, just as McFarland[1] has shown for abnormal involution of the breast.

In this category blastomycosis probably belongs, as we have to do here with chronic suppuration with multiple sinuses which, in principle, may be regarded as ulcers. The most extreme acanthoses develop in this condition, some positions being quite indistinguishable, morphologically, from cancer. The discovery of the microorganisms, of course, settles the case; but oftentimes these are scarce, and one must depend upon the associated miliary abscesses for final diagnosis. The latter are almost invariably present, comparatively characteristic, and a most welcome aid in the diagnosis of this disease. In fact, the miliary abscesses will generally convey the hint to the pathologist as to the nature of the condition long before he identifies the microörganism.

Molluscum contagiosum is another hyperplastic disease which has been mistaken for neoplasia. Its appearance is characteristic and diagnostic *per se*. In ordinary acanthosis the form of the normal interpapillary peg is more or less maintained and the hyperplasia, as a rule, extends widespread and diffusely over the surface of the skin. The molluscum contagiosum lesion is sharply localized and the interpapillary pegs, if they may be designated such, extend downward as lobules which at first sight suggest those of sebaceous glands. The older designation, epithelioma contagiosum, is not at all appropriate. Never is there any invasion of the tissues or metastasis, and the disease yields readily to the simplest form of treatment. The practical point for the pathologist is that it may be mistaken for squamous-cell cancer.

Sweat Ducts. The lining epithelial cells of these structures readily undergo hyperplasia and also metaplasia in the presence of surrounding acute inflammatory processes, particularly when attended by suppuration or near suppuration.[3] Normally, the sweat ducts are lined by two layers of low cuboidal epithelium and have an extremely delicate lumen. Under the influence of the stimuli just mentioned the numbers of cells will not alone multiply, but the cells will undergo metaplasia into a large, broad, squamous-epithelium-like cell. These cells, projecting beyond the basement membrane, will produce a clumsy, irregularly outlined cylinder instead of the delicate, graceful one of the normal sweat duct. This, again, has been mistaken for squamous-cell carcinoma, the threadlike lumen of the structure being overlooked. I have observed this change in erysipelas, in suppurating syphiloderms and in skin adjacent to discharging sinuses.[3]

Syringoma. This is commonly included under the general heading of "benign cystic epithelioma." It appears in the form of small cysts, usually originating deep into the corium, or solid strands of cells which twist more or less and suggest an origin in the sweat glands. Strands of cells frequently pass from these structures and

permeate the surrounding tissue. Histologically, they might easily pass for scirrhous adenocarcinoma. Clinical experience, however, has shown that these lesions have none of the malignant propensities of carcinoma; they never metastasize, rarely ulcerate and never induce cachexia. Without such an opportunity as presents itself in the skin for direct clinical observation of the disease over a long period the real nature of syringoma might never have become known. Indeed, there are good reasons for believing that the condition is a nevus in the Cohnheim sense, analogous to the carcinoid of the appendix.

Trichoepithelioma. This is another lesion which has been classified under the general group of the benign cystic epithelioma. As its name indicates, it has its origin in the hair follicle; strands of cells are seen extending from the neighborhood of a follicle into the surrounding lymphatic spaces. It is possible to trace actual connection between these strands and the hair follicle. The same considerations as to hyperplasia and neoplasia hold here as for syringoma.

Sebaceous Glands. These occur in increased numbers and at least give the appearance of hyperplasia in certain localized areas which are known as seborrheic nevi. But acquired hyperplasias are comparatively rare for the sebaceous gland; even where there are marked suppurative conditions its cells do not appear to have a high level of reactivity. Because of the varying size, even under normal circumstances, of different sebaceous glands, precise estimates of increases are generally difficult or impossible. Certain it is that the type of sebaceous glands normally indigenous to the particular body part concerned must be taken into account, and that a hyperplasia can only be positively declared when the increases are of high grade or extreme. A rather lonely example of genuine hyperplasia is seen upon the face in connection with rosacea and rhinophyma. These hyperplasias are generally associated with Demodex folliculorum. The tendency in the past has been to discount the significance of the parasite in the production of the hyperplasias; however, an English publication[4] has of late revived the subject by reporting them in a definite majority of breast cancer. Whatever be the relation to demodex to the hyperplasia, it remains that the sebaceous glands are among the least liable of the cutaneous structures to hyperplastic changes; when seen, they occur in connection with chronic rather than acute inflammatory processes.

Carcinoma of Pluricentric Origin.—It is, of course, well known that in the ordinary epidermal carcinoma the neoplastic invasions extend from the epiderm. I do not believe, however, that it is generally appreciated that similar extensions may pass from three different places in one and the same section and at the same time; that is, from the epiderm, hair follicles and sweat glands. I have seen 2 such cases, 1 of which is illustrated herewith. The point here is that whatever the cancerous influences may be, they are telling

alike upon all 3 of these skin structures. This has an application to the unicentric and pluricentric origins of carcinomas, and the writer agrees with Adami,[5] that some tumors at least are pluricentric. The skin is a particularly favorable organ for demonstrating pluricentricity, because the different derivatives of the ectoderm are different morphologically and can be readily identified. While in such cases it must be conceded that the carcinoma "virus" was playing upon different anatomic structures, it is obvious that it was selecting the *least specialized* parts of the ectodermal derivatives; seldom do we see carcinoma of sebaceous glands or of the secretory parts of the sweat glands.

Nevocarcinoma. It may be inquired, after the discussion of the nevi above, what the criteria may be for the histologic diagnosis of nevocarcinoma, particularly in its early stages. The situation is, indeed, most difficult. The usual histologic criteria seem to fail us in differential diagnosis because nevus cells are ordinarily large and embryonal and lie loosely and disjointedly in the fashion of carcinoma. The only refuge that the writer knows is experience with a sufficient number of nevi to have a conception of the extent to which they may "normally" vary, both as to arrangement and structure of cells. If, thereafter, the cells of a nevus are found to be different, it may be surmised that the untoward changes are those of carcinoma. The writer has studied such a case in which a rarefaction of cytoplasm was the new form assumed by the cells in addition to exhibiting mitotic figures. The rarefaction might have been interpreted as an hydropic degeneration, but there were no associated changes harmonizing with such an idea, and it was concluded that it reflected an inherent *physiologic* perversion. Furthermore, the cells extended downward into the corium from the epiderm in a directly perpendicular, parallel fashion, such as is not commonly seen in nevi. In this case it was then a variation in the arrangement of cells as well as of the cytology itself that established the diagnosis which was verified later at necropsy.

Conclusions. The skin is particularly favorable for studying the life history of congenital anomalies (nevi) because they can be followed by the eye and otherwise from their very beginnings. Pigmented nevi which are known to be benign clinically may appear carcinomatous as judged by general pathologic criteria. Benign anomalies of the sweat glands and hair follicles may likewise appear in the form of carcinoma histologically (benign cystic epithelioma).

The human epiderm has the capacity (developed perhaps phylogenetically) of regenerating so vigorously that it may simulate cancer. In the presence of known chronic cutaneous defects the significance of epithelioma-like hyperplasia should be heavily discounted. Deep permeation below the level of the sweat glands, and mitoses are the only certain histologic criteria in some cases.

Sweat-duct epithelium readily becomes hyperplastic in connec-

tion with suppurative and other irritative processes. It may be sufficiently irregular to suggest carcinomatous change.

The secretory portions of the sweat glands are singularly exempt from hyperplastic tendencies, even when surrounded by leukocytic infiltrates and when the ductal epithelium is hyperplastic. Neoplasia is excessively rare.

Rarely do the sebaceous glands become neoplastic. They are said to become hyperplastic in rosacea and seborrheic states, but it is difficult to separate hyperplasia from overdistention and overactivity in these states. A genuine hyperplasia does occur in a few chronic conditions, in which case Demodex folliculorum is likely to be found associated. The relation of cause to effect in the latter connection is not established—the door is open either way.

In the case of the skin, the accessibility to direct clinical observation has been the factor which has finally set the physician aright concerning the nature of several diseases; without this and considering only the histopathology, an entirely erroneous opinion could have been arrived at. The skin is, therefore, recommended as a field to be more extensively used in experimental medicine.

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EXCISION OF PROSTATIC BAR BY THE CUTTING CURRENT.

By Clyde W. Collings, M.D.,
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During the past four and a half years, we have, at Bellevue Hospital and New York University, relieved fibrous obstructions at the bladder neck, by the cutting high-frequency current, in 55 patients. The high-frequency apparatus we employ, the so-called "electrotome," is similar in principle to the spark-gap machine used to fulgurate bladder tumors. The rate of high-frequency oscillation is "stepped up" about fourteen times. This current cuts instead of burning and so leaves only a thin slough. The bleeding at the time of operation is unimportant, and there is no late secondary hemorrhage. Hence the current may be applied through the endoscope without opening the bladder.

We reported 25 patients of this group before the American Urological Association in 1926.[1] We now wish to tell of our results upon the 34 patients operated upon recently.

We employ this operation on three types of bladder-neck obstruction.

1. Fibrous contracture and bar (congenital or acquired).
2. Fibrous scar following prostatectomy.
3. Carcinomatous bar, resulting from a carcinoma of the prostate.

We do not employ this procedure on any type of adenomatous hypertrophy of the prostate. Prostatectomy is the method of choice in dealing with this form of obstruction.

To see what would happen, we tried the cutting current on 4 cases of adenoma. We failed to cure the patients. All 4 have required subsequent prostatectomy.

We have modified Doctor McCarthy's panendoscope by placing a small, metal tube from the inlet faucet to the end of the sheath. The water, after circulating in the posterior urethra and bladder, flows out through the other faucet, thereby giving continuous irrigation. The modification helps to speed up the operation for: (1) The water distending the bladder is being constantly changed; (2) air bubbles and any instrumentation bleeding are washed away; (3) a constant fixed distension of the urethra and bladder may be maintained.

The majority of patients are given a caudal anesthetic (30 cc. of 2 per cent novocain). Some require gas or spinal anesthesia.

The technique of the operation is as follows: The rheostat of the apparatus is placed on 1 or 2. The spark-gap lever opened about $\frac{1}{4}$ of an inch. The current may be increased by moving the rheostat on 2 or 3 and opening the spark-gap lever about 2 inches. We do most of our operations within this range. The electrode knife is engaged upon the bladder neck at "6 o'clock" and slowly pushed in and out between this point and the verumontanum. Continuing in this manner the incision is widened and deepened as small bits of tissue are shaved off.

It is usually more convenient to place the electrode in position and move the electrode and urethroscope *en masse*. We take five or ten minutes to cut to an approximate depth of 1.5 cm. The gutter is widened by placing the electrode at "5 o'clock" and cutting back-and-forth toward the verumontanum. Then the knife is engaged at "7 o'clock" and the incision extended backward to the same point, the same depth attempted as in the primary cut. Small tufts of white tissue are seen sticking up between the incisions. These may be sawed off by turning the knife blade sideway. The primary cut is the all-important one.

The procedure should be done with precision, taking perhaps twenty or twenty-five minutes, the electrode moved slowly, and the cut made deeply. When the bladder neck is properly excised, the

base of the verumontanum, the valley in the posterior urethra, and the trigone should be on the same horizontal plane. The obstructing bar has been entirely whittled away.

A word of caution: The electrode should not be brought in contact with the sheath, as a slight short circuit is produced. (The patient notices a pricking sensation in the urethra.) It is better to use dry cells for cystoscopic illumination to further eliminate the possibility of a short circuit.

The 34 case histories were tabulated as follows:

TABLE I.—CLASSIFICATION AS TO DIAGNOSIS.

	Patients.
Fibrous bar and contracture	25
Carcinomatous bar (prostatic carcinoma)	6
Fibrous scar after prostatectomy	3

The age varied from twenty-five to eighty-nine years. There was 1 patient in the second decade, 4 in the third, 5 in the fourth, 8 in the fifth, 9 in the sixth, 6 in the seventh, and 1 in the eighth. The usual complaints were frequency, burning, difficulty, and marked urgency. Nine patients had complete retention.

In the bar and contracture cases the prostate by rectum felt small, irregular and firm throughout. When the instrument was passed into the bladder an obstruction at the vesical outlet was encountered. It was often necessary to depress the ocular end of the urethroscope to get by the bar. A definite elevation of the floor of the bladder neck was seen as the instrument was withdrawn into the posterior urethra. In 15 cases, a marked bas fond was noted with the accompanying tilting of the trigone, and difficult visualization of the ureter orifices.

TABLE II.—STATUS BEFORE AND AFTER OPERATION.

Residuum before operation:	Patients.
Complete retention	9
All urine through suprapubic fistula	2
From 120 cc. to 1500 cc.	9
From 30 cc. to 100 cc.	14
Total	34
Residuum after operation:	
From 15 cc. to 30 cc.	8
No residuum	22
Unimproved cases	2
Undetermined cases	2

The patient with the 30-cc. residuum on May 4, 1927, had 760 cc. before operation on January 25, 1927. It sometimes takes several months before the maximum effect of the operation is attained.

The group without residuum includes patients with a residuum before operation, varying in the individual case from 30 cc. to complete retention.

The 2 unimproved cases were the following:

W. U., aged sixty-eight years, referred by Dr. Veenstra, with complete retention from carcinoma of the prostate, was operated upon July 9, 1926. A retention catheter was used for three days after operation; has voided continuously after its removal, with 180-cc. residuum. Died of pneumonia on the eleventh day after operation.

A Bellevue patient, P. K., aged eighty-nine years, with carcinoma of the prostate, died two weeks after operation from generalized carcinomatosis. The postmortem showed a wide valley about 2 cm. deep from the bladder neck to the verumontanum, the surface of the wound was grayish-yellow with a few areas of phosphatic incrustation. The area of slough extended down into the tissues from 1 to 2 mm.

The 2 undetermined cases were the following:

M. W., aged seventy-three years, with a residuum of 240 cc. before operation, was operated upon December 14, 1926, for a carcinomatous bar. He died of pneumonia nineteen days after operation. The patient's physician in the country reported no difficulty with urination forty-eight hours before death. At this time he developed complete retention.

I. R., aged forty years, had a suprapubic cystotomy, July, 1925, for vesical calculus by another surgeon. A suprapubic fistula persisted. A prostatic bar was excised January 4, 1927. He was then lost track of until May 11, 1927. At this time his doctor reported the abdominal wound closed, the urine passed more freely, the residuum less, the exact amount undetermined.

The operative results of the 25 patients reported in 1926 have persisted up to now (September, 1927) except in 2 cases. Some cases have gone as long as three years. The 2 exceptions have been operated upon successfully a second time for further reduction of the residuum.

Postoperative Treatment and Complications. 1. An indwelling catheter is tied in the urethra of a patient with complete retention or a residuum over 200 cc.

2. The bleeding after operation has never been more than enough to color the urine. A minority show small clots the size of a small grape, for the first week or ten days.

We recently operated upon 3 patients in our office. Two patients had an uneventful convalescence; the third had to be sent into the hospital for several days with an indwelling catheter to control the bleeding. It is better to do this operation in a hospital, and keep the patient quiet for a day or two afterward.

3. In order to control infection, postoperative intermittent catheterization and bladder irrigation have been employed in a number of cases. This sometimes excites bleeding. For patients with less than 200 cc. residuum before operation do not catheterize for two

weeks. For patients with a residuum of more than 200 cc. use an indwelling in the urethra for three days after operation. After removal, the residuum gradually diminishes.

4. Burning, during and at the end of urination, may be present off and on for two or three weeks, rarely three or four.

5. Two of our patients developed epididymitis.

Summary. 1. The cutting high-frequency current, will efficiently excise fibrous, scar and carcinomatous tissue at the bladder neck.

2. We have relieved 55 patients of their bladder-neck obstruction by this direct-vision method. Two patients died of pneumonia, 1 of carcinomatosis, and of 1 there is no record of the present residuum.

3. The current cuts instead of burning, hence there is no thick slough to separate off and no secondary hemorrhage.

4. Primary bleeding has never been more than enough to make the urine sherry-colored with small clots at times.

5. This procedure changes the operative risk from major to minor, or the difference between a suprapubic cystotomy and a cystoscopy.

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THE EXAMINATION OF FLUIDS FOR TUMOR CELLS.

An Analysis of 113 Cases Checked against Subsequent Examination of Tissue.

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The examination of transudates and exudates for the presence of neoplastic cells is a recognized laboratory procedure today and the report "Tumor cells present" or "No tumor cells found" is a valuable part of the data upon which the clinician bases his diagnosis. Not many years ago, however, such a report was made but rarely and then with no great confidence, since there were neither standard technique for making such examinations nor definite criteria for calling a group of cells neoplastic. The technique which is used today in nearly all laboratories was devised in 1900 by the late Dr. F. S. Mandlebaum, Pathologist of The Mount Sinai Hospital of New York City, and marked a distinct advance in the handling of fluid specimens of all kinds. The criteria for considering cells neoplastic have arisen gradually out of the careful studies of many observers over a long period of time.

Attempts to identify cells from a neoplastic source date back to 1860, when Beale[1] noticed large multinucleated cells, single, and in clumps, in unstained smears of sputum from a case of carcinoma of the pharynx. Nine years later Ashworth[2] described cells in the blood stream in a patient with multiple skin tumors, which he declared to be neoplastic cells. Both of these cases remained as curiosities until Quincke,[3] in 1875 published his careful chemical, physical, and histologic observations on chylous ascitic fluids. He demonstrated that the milkiness of cancerous ascitic fluids was not due to fat but due to an albuminous substance, probably from the neoplasm (carcinoma cells?). The following year Hampeln[4] reported finding a shred of tissue in the sputum of a patient, one of whose extremities had been amputated for sarcoma three years before. Examination of the shred revealed sarcoma, and brought to his attention the importance of the search for minute particles of tissue in fluid specimens. In 1882, Quincke[5] reported on the examination by means of stained smears of a large series of peritoneal and pleural fluids in cases of inflammatory as well as neoplastic conditions. Besides noticing the preponderance of leukocytic cells in inflammatory exudates and of mesothelial cells in tuberculous and cancerous effusions, he described in one ascitic fluid clumps of large irregular cells containing vacuoles. This case was considered at first to be one of cirrhosis of the liver, but from the presence of these cells the diagnosis of peritoneal carcinosis was entertained, and this was proven to be correct at autopsy. This case is the first in which the examination of a transudate was of distinct diagnostic value, and it aroused the interest of pathologists everywhere in this new and important laboratory method.

The same year, Ehrlich[6] added new impetus to the examination of smears of blood and exudates by the introduction of new fixing and staining methods. In his monumental work on the morphology of cells in all types of fluids, Ehrlich included three cases of intra-abdominal carcinosis, in which the diagnosis had been suggested by the finding of highly atypical cells in the peritoneal fluid. During the next thirteen years only two brief reports appeared. One was by Huber,[7] who found, as had Hampeln fourteen years before, a shred of neoplasm in the sputum of a patient suffering from sarcoma of the lung. The other was by Prentiss,[8] who detected a small particle of tumor tissue in a smear of a pleural fluid.

In 1895, Rieder[9] reported the results of the examination of a large number of stained smears, and recorded in the peritoneal fluid of a case of carcinoma of the ovary many large vacuolated cells with mitotic figures. This was the first time that cells free in a fluid medium were seen undergoing mitotic division. In discussing this most important observation, Rieder suggested that the consistency of the tumor determines whether fragments shall break off and continue to live in the surrounding medium. Rieder was also

concerned with the histologic differentiation of neoplastic from mesothelial cells. His remarks at that time hold good today: "It is understood that the finding of numerous polymorphous, unequal, large cells especially when they have vacuoles and lie in clumps, speaks more for neoplastic than for mesothelial cells, but the diversity of form of mesothelial cells in inflammatory processes in serous effusions is misleading."

In the same year, Bahrenberg[10] published his observations on the examination of fluids by a new method. He remarked on the inadequacy of fresh and dried smears, either stained or unstained, and described a technique which was the precursor of that which will be shortly described. Bahrenberg allowed a large quantity of fluid to stand and clot spontaneously. After pouring off the supernatant fluid, the clot was shrunken and hardened by successive additions of alcohol, until a small stringy mass was obtained. This was finally embedded in celloidin and cut like tissue. With the aid of this technique Bahrenberg was enabled to find epithelial cells in two ascitic fluids in which autopsy later revealed carcinoma involving the peritoneum. The significance of Bahrenberg's method is obvious. It is regrettable that his work was buried in an obscure journal and was apparently unknown to any of the men who later attacked the subject. This year also saw the report of Betschart,[11] whose finding of atypical cells in stained smears of sputum and ascitic fluids served to corroborate the same observations of previous observers.

The next important publication on this subject was by Dock, in 1897. But before describing his work it is of interest to note that in the year before, two textbooks on pathologic technique had appeared containing carefully guarded statements about the examination of serous fluids for tumor cells. Geigel and Voit[12] stated that abnormal cells may be found in fluids and that mitoses are of great significance. Eichhorst[13] said that particles of tumor tissue may be found in the sputum, and that in carcinoma of the pleura, cells with multiple nuclei, characteristic of cancer, occur "not rarely." Dock[14] made a very careful study, by means of stained smears, of the atypical cells found in a pleural and an ascitic fluid. He described and pictured beautifully the most striking variations in size, shape, and nuclear arrangement which these cells presented, and described many atypical mitotic configurations. Dock was not satisfied that these abnormal cells were characteristic of carcinoma and studied many other fluids for comparison. In a pleural effusion following appendicitis, he observed the same cells with the most bizarre abnormalities, only in very small quantities. From our present knowledge his conclusion, that the difference between the cellular contents of carcinomatous and inflammatory effusions is one of quantity rather than quality, cannot be accepted. How much the technique had to do with the production of bizarre

cell shapes and nuclear configurations makes an interesting speculation, since it is well known that smearing and drying give rise to marked distortion of cell and nuclear outlines. In the same year, Warthin[15] described spindle cells floating free in the pleural fluid in a case of fibrosarcoma of the pleura, and, in 1899, Benecke[16] reported pigment-containing cells in the peritoneal fluid from a case of melanocarcinoma.

Steiner,[17] in 1901, found, in an ascitic fluid, a shred of tissue large enough to embed and cut. It showed adenocarcinoma, whereas ordinary smears from the fluid revealed no abnormal cells. From this one case he concluded that the examination of fluids for tumor cells is useless unless macroscopic particles appear in them. He quoted Dock's finding of the similarity of cells from malignant and nonmalignant sources as further proof of the unreliability of this method of examination. It is interesting to note that he is the only one to quote Bahrenberg's new method of examination, and decried it without even testing it. His work is only significant in that it shows the importance of even minute shreds of tissue. A fragment of tissue with orderly arrangement of cells and stroma goes much further toward the diagnosis of cancer than a great many isolated cells, however abnormal they may look. Having realized long before the importance of isolating small fragments of tissue and having tried all methods and found them unsatisfactory, Mandlebaum[18] devised a method which will be described later and, in 1900, made it the subject of a brief report describing actinomyces found in pus by means of his new technique.

As if in answer to the skeptical article of Steiner, the next ten years brought forth a host of papers describing the findings, in one or a few cases, of cells from a neoplastic source. (See references 19 to 35 inclusive.) Only five of these authors reported the presence of mitotic figures, the others basing their diagnoses on alterations in size, shape, staining quality, and nuclear arrangement of the cells seen. All of these observers used stained smears, and appeared to consider them adequate. During this ten-year period the fifth edition of Lenhartz's textbook on laboratory technique appeared and summed up the feeling at that time concerning the presence of neoplastic cells in body fluids. Lenhartz[36] states that the finding of villous fragments, colloid masses, and shreds of papillary tumor often yields the diagnosis, but in their absence "we must emphasize the importance of the abundant appearance of large cells manifesting marked morphologic variations."

In 1911, Warren[37] reviewed the literature up to his time and added some very significant observations of his own. Commenting on the finding by Dock of mitotic figures in nonmalignant effusions, he stated that neither he nor anyone else had been able to repeat this observation. From a review of the reports of others, he considered the finding of mitotic figures rare enough even in cells from

malignant effusions. He added five cases of his own, all verified by autopsy, in which the discovery of cells in a serous effusion established the diagnosis during life. Warren's work probably represents the best of that accomplished by means of stained smears. The fact that he did not mention finding small tissue fragments is significant when we consider that these most helpful bits of evidence are nearly always destroyed in the process of smearing. In 1917, Mandlebaum[38] in a brief report redescribed the technique which he had devised sixteen years before and emphasized that by this method the most minute fragment of tissue was revealed and all cellular relationships carefully preserved. It is interesting that the same method was hit upon independently by Ellis,[45] in the laboratory of the Memorial Hospital just before this brief report appeared. At about this time other laboratories commenced to use the method as well.

From 1917 to the present day there has been but little published on the subject. Josephson[39] described fragments of tissue found in serous fluids and emphasized their importance. Quensel[40] described a new smear technique where stain was added to the fresh centrifugate and the smears examined before drying. In his hands this method seemed to give excellent results and he emphasized the presence of deep-staining nucleoli as evidence of the neoplastic nature of a cell. Even as late as 1922, agreement was not complete as to the value of examining fluids for tumor cells. Apparently unaware of any but the smear technique, Panton[41] reported the finding of sarcoma cells in a cerebrospinal fluid and, although successful in his one case, condemned the whole method on the grounds that "tumor cells do not usually become detached from tumors" and that "fragments of tumor resemble clusters of endothelial cells." That there is no basis for these beliefs will be shown later on in this paper.

Within the past four years, Levesque[42] and Feinblatt[43] each reported a case in which cells were found in serous effusions, but by far the most important contribution is that of Seecof and Boetch.[44] These observers studied serous effusions from a series of cases by means of an embedding technique similar to the one which I will describe, and attempted to evaluate the method along the same lines as any other laboratory procedure. By comparing their cases with autopsy findings in a few instances and final clinical diagnoses in the remainder, they found a high degree of accuracy where it was possible to give a positive report. Conversely the negative report meant very little. In this regard, they likened the examination of serous effusions for tumor cells to that of sputum for tubercle bacilli. They also emphasized the difficulty of differentiating mesothelial cells in long-standing effusions from tumor cells and the errors which they reported fell into this category. Their results will be compared with mine at greater length later on.

Technique. The technique is a very simple one. The fluid in a large Erlenmeyer flask is allowed to settle by gravity, by standing overnight. The clear upper layer is poured off and as large a quantity of the cloudy sediment as can be conveniently handled is centrifuged in a wide tube, (capacity 50 cc.) tapering to a point. This is centrifuged at moderate speed for at least twenty minutes. The supernatant fluid is poured off without disturbing the sediment, and the tube is filled with 10 per cent formalin. This is allowed to stand for twenty-four hours, when the formalin is poured off. By this time, the sediment is sufficiently hardened to be removed from the tube without falling to pieces. It is gently separated from the tube with a thin blade, lifted out with forceps, and cut from above downward, in order to obtain all layers of the sediment (Fig. 1).

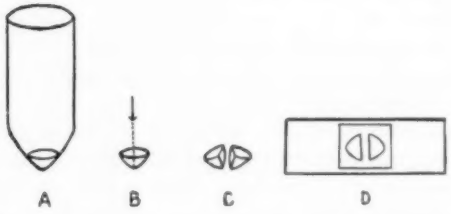

FIG. 1.—Technique of preparing sections. *A*, tube containing sediment after centrifuging; *B*, "button" of sediment removed from tube showing plane of section; *C*, "button" sectioned. Two opposing faces to be cut after embedding. *D*, appearance of finished slide.

This is important, as tumor cells may be missed by cutting only the top or bottom layers. The two halves are then hardened in graded alcohols, run through chloroform paraffin, embedded in paraffin, cut, and stained by hematoxylin and eosin or hematoxylin alone. The single hematoxylin or iron hematoxylin stain gives sections of remarkable clarity and was preferred by Dr. Mandlebaum in all tissue work.

Review of Examinations made at Mount Sinai Hospital in Past Fifteen Years. Since 1900, some 2000 examinations have been made, but since complete records are not available on private cases nor on ward cases before 1912, I have chosen to investigate only those examinations made on ward patients during the past fifteen years. The number of examinations of the same or different fluids on the same patient varied from one to thirteen and thus is no index to the number of patients examined. The great majority of the patients had only a single examination and this fact alone can be held accountable for some of the errors which will be mentioned later. The following table (Table I) gives the type and number of fluids examined with their respective reports since 1912.

In order, however, to make this report as accurate as possible, only those cases have been included in this analysis which came to

autopsy or operation, or had a biopsy performed. This automatically excluded a large group in which the clinical evidence in favor of or against the presence of a neoplasm was irrefutable, but the added accuracy thereby obtained was deemed more important than an increase in numbers. The following charts give the number of examinations per case and the number of cases verified by each method.

TABLE I.—TYPE AND NUMBER OF FLUIDS EXAMINED IN PAST FIFTEEN YEARS.

Type of fluid.	Examinations.	Reported "tumor cells found."	Reported "no tumor cells found."
Abdominal fluid	237	72	165
Pleural fluid	489	83	406
Sputum	80	2	78
Urine or bladder-washings	46	2	44
Gastric contents	28	4	24
Hydrocele fluid	7	1	6
Cerebellar cyst fluid	7	0	7
Pericardial fluid	4	1	3
Miscellaneous	16	0	16
Total	914	165	749

TABLE II.—NUMBER OF EXAMINATIONS PER CASE.

No. of cases.	Examinations, per case.	Total examinations.
93	1	93
8	2	16
9	3	27
1	4	4
1	6	6
1	13	13
Total 113		159

TABLE III.—METHOD OF VERIFICATION.

Source of tissue.	Cases.
Autopsy	65
Exploratory operation	39
Biopsy	9
Total	113

When a fluid on one occasion had been reported negative and on another occasion positive, the case is considered a positive one in much the same way that one positive smear for tubercle bacilli outweighs a dozen negative ones. To simplify further this analysis, all cases in which the fluid was reported "doubtful" or "questionable," were considered negative, and those reported "highly suggestive," positive. It is interesting that equivocal reports were very rarely sent out as it was usually possible to make a definite report of "tumor cells present" or "tumor cells not found." Table IV compares the report as issued with the findings at autopsy, operation, or biopsy, giving also the fluid examined and separating the positives from the negatives.

TABLE IV.—COMPARISON OF REPORT WITH SUBSEQUENT EXAMINATION OF TISSUE.

Type of fluid.	Cases reported positive.	Verified.	Disproved.	Accuracy, per cent.	Cases reported negative.	Verified.	Disproved.	Accuracy, per cent.
Abdominal fluid	24	20	4	83	30	18	12	60
Pleural fluid	10	9	1	90	25	9	16	36
Sputum	1	1	0	..	4	1	3	
Urine or bladder washings	1	1	0	..	7	1	6	
Gastric contents	1	1	0	..	4	0	4	
Hydrocele fluid	1	1	0	..	2	2	0	
Cerebellar cyst fluid	0	0	0	..	1	0	1	
Pericardial fluid	1	1	0	..	0	0	0	
Miscellaneous	0	0	0	..	1	0	1	
Totals	39	34	5	87	74	31	43	41

It is readily seen that the positive report carries with it a high degree of accuracy (87 per cent), while the negative is of little value. In this respect, the examination of fluids for tumor cells differs in no respect from any other laboratory procedure. However, a careful study of the cases which were reported positive and shown later to have no tumor, and those reported negative which were proved to have a tumor, has taught many valuable lessons which should increase the degree of accuracy in the future. Before taking up a detailed analysis of the above cases, it might be worth while to examine a few representative slides and state the criteria used in reporting them positive or negative.

An occasional fluid shows complete layering of its cellular elements. Red blood cells, if present, are usually at the bottom with the mesothelial cells next and the white blood cells on top (Fig. 2). Tumor cells may be present in any or all of these layers, depending upon their specific gravity. No aid can, therefore, be expected solely from the position occupied by the cells suspected of being neoplastic. It is in a fluid of this type that a clump of abnormal cells can be readily recognized, since all the surrounding cells are of one definite variety, but unfortunately this particular picture is rare (Fig. 3). The majority of fluids show no layering at all, but present an even admixture of cells of many types embedded in a pale protein coagulum. These are by far the most numerous, and it is here that a small fragment of tissue or a glandular acinus gives the clue instantly, when isolated cells are not definite enough (Fig. 4). Such a fluid may be studded with small clumps of deeply staining cells, slightly larger than the surrounding blood or mesothelial cells, giving a dotted or mottled appearance to the slide. Indeed,

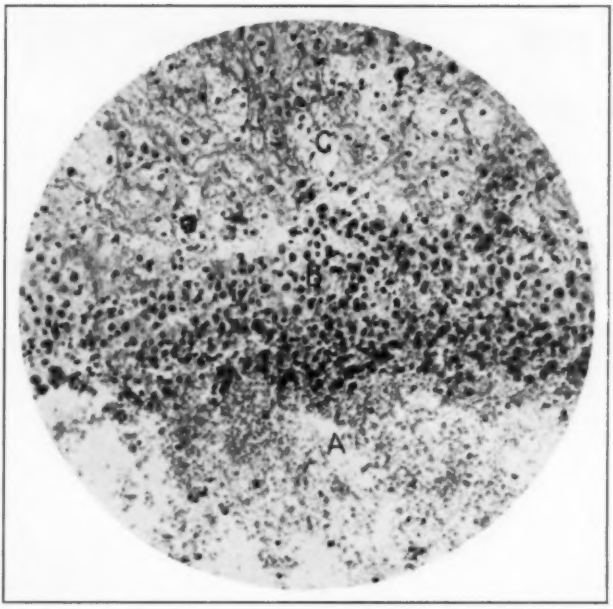

FIG. 2.—Pleural fluid from a case of inflammatory disease of the pleura to show layering of the cellular elements. (× 200). *A*, red blood cells; *B*, mesothelial cells; *C*, leukocytes.

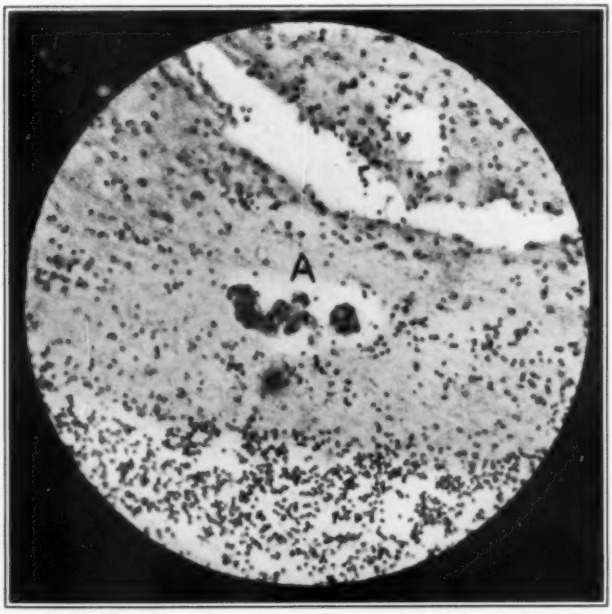

FIG. 3.—Ascitic fluid from a case of papillary adenocarcinoma of the ovary. (× 100). *A*, fragment of tumor tissue surrounded entirely by lymphocytes.

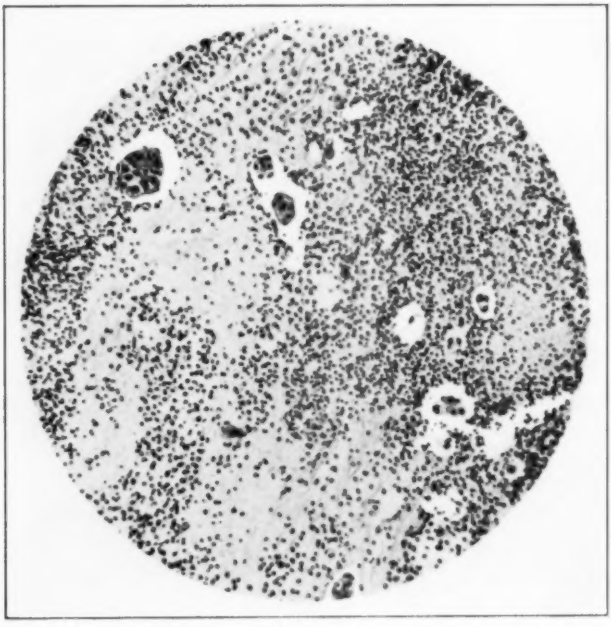

FIG. 4.—Ascitic fluid from a case of intra-abdominal carcinoma. (× 130.) Shows many fragments of tumor tissue and clumps of tumor cells surrounded by many lymphocytes, polymorphonuclear leukocytes and red blood cells, and relatively few mesothelial cells.

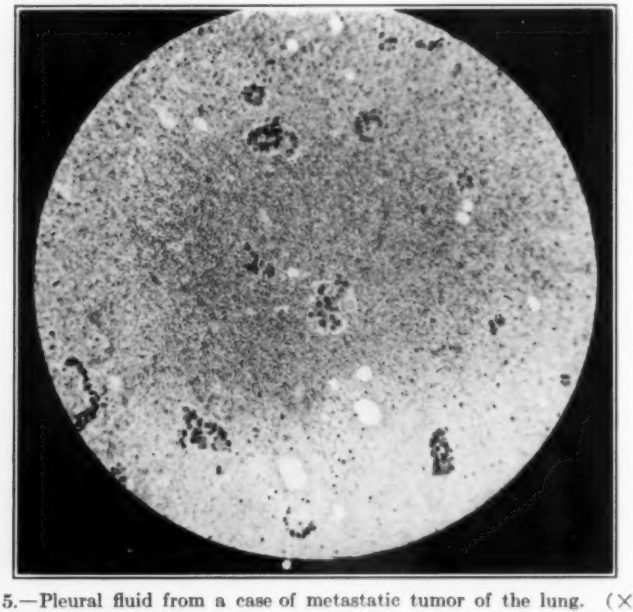

FIG. 5.—Pleural fluid from a case of metastatic tumor of the lung. (× 100.) Shows many fragments of tumor tissue and clumps of tumor cells giving a mottled appearance to the section under lowest magnification.

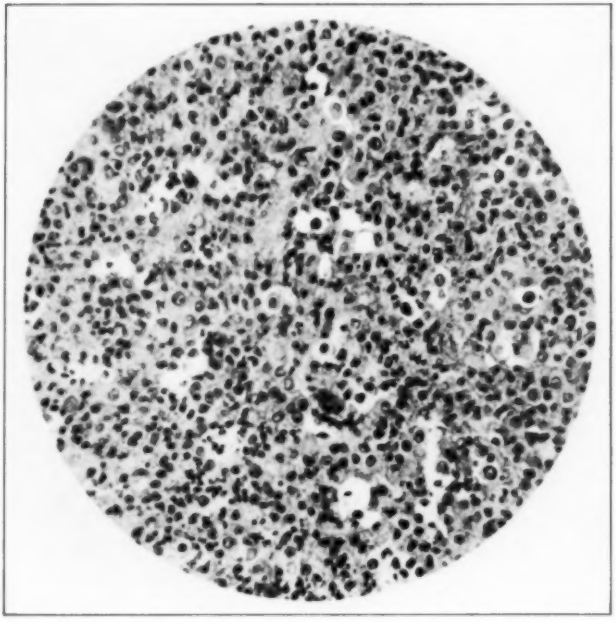

FIG. 6.—Long-standing ascitic effusion from a case of cirrhosis of the liver. (× 250.) Shows sheets of mesothelial cells studded with lymphocytes and polymorphonuclear leukocytes. The mesothelial cells group themselves around fat droplets and contain many vacuoles.

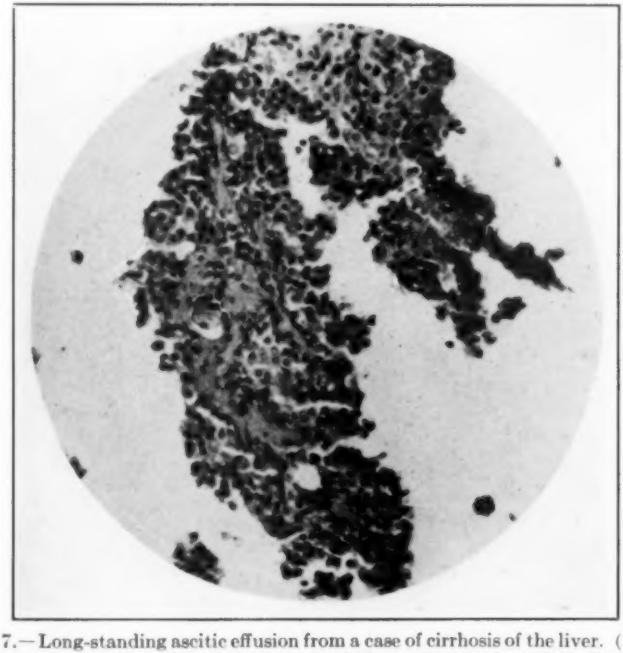

FIG. 7.—Long-standing ascitic effusion from a case of cirrhosis of the liver. (× 250.) Shows mesothelial cells arranged along a strand of protein coagulum giving the appearance of papillary tumor. Note the lack of fibrillar structure in the "stroma."

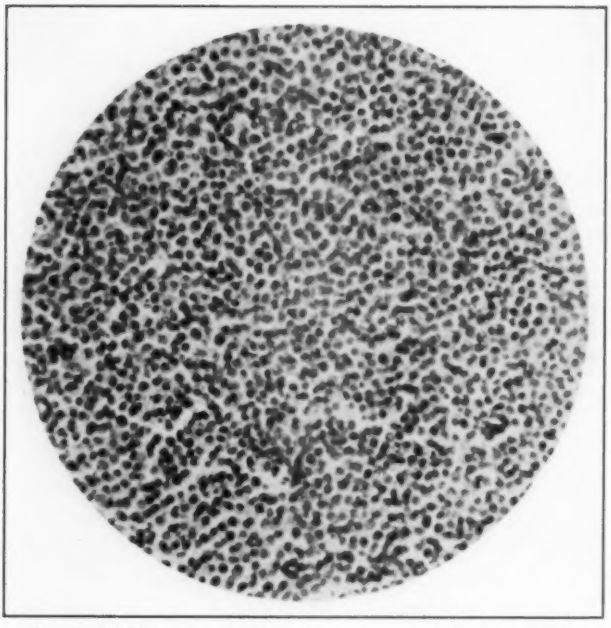

FIG. 8.—Ascitic fluid from a case of lymphosarcoma of the small intestine. (× 250.) Shows large number of tumor cells with a few scattered polymorphonuclear leukocytes. Individual tumor cells are all alike and suggest lymphocytes except that they are slightly larger, have more cytoplasm and contain occasional mitotic figures.

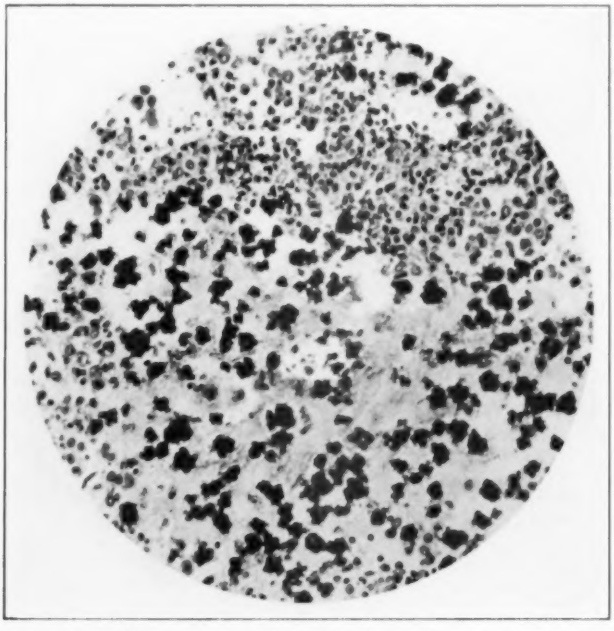

FIG. 9.—Ascitic fluid from a case of cirrhosis of the liver. (× 200.) Deep black areas are colonies of bacteria. Extreme irregularity, granular appearance and lack of cell membranes distinguish them from cells.

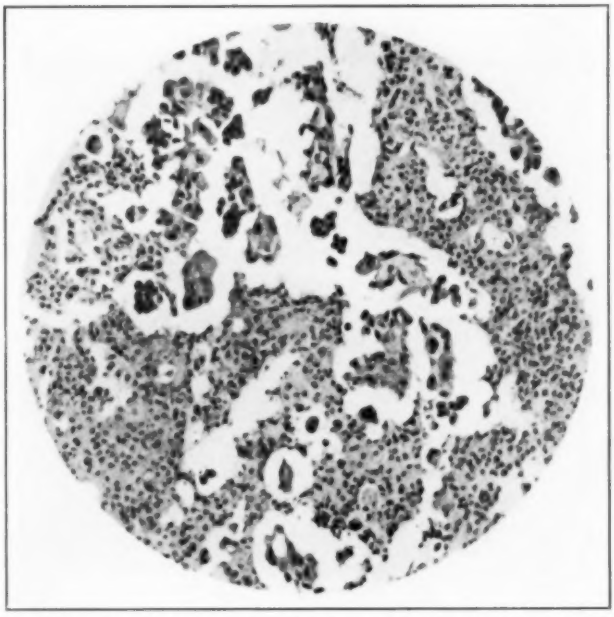

FIG. 10.—Pleural fluid from a case of primary alveolar carcinoma of the lung. (× 150.) Fragments of tumor tissue and clumps of tumor cells identical with those of primary tumor. (See Fig. 11.)

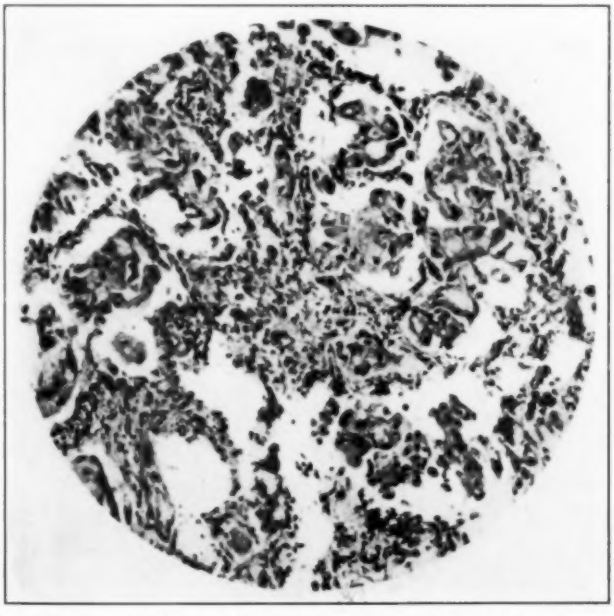

FIG. 11.—Section of primary alveolar carcinoma of the lung from the same case as Fig. 10. (× 150.) Tumor tissue for comparison with cells in pleural fluid. (See Fig. 10.)

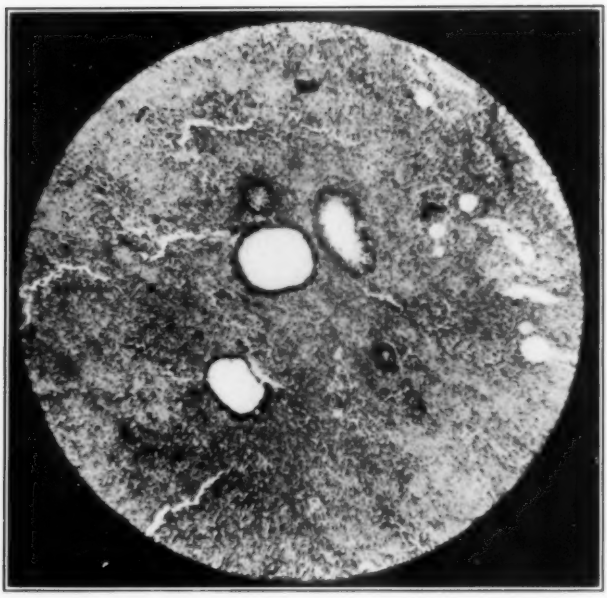

FIG. 12.—Ascitic fluid from a case of intra-abdominal papillary adenocarcinoma. (× 100.) Note similarity of acini in fluid with original tumor. (See Fig. 13.)

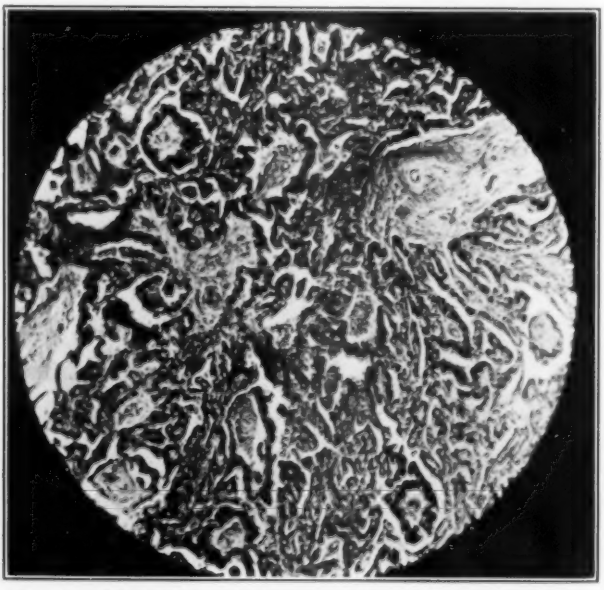

FIG. 13.—Section of intra-abdominal tumor of same case as Fig. 12. (× 100.) Tumor tissue for comparison with cells in ascitic fluid. (See Fig. 12.)

this mottling, due to the practically invariable rule that tumor cells stain more deeply than others, is an important factor in deciding whether they are present or not. Often such a decision may be made under the low power of the microscope with perfect surety (Fig. 5). It is in the interpretation of a single cell or one small area of apparently abnormal cells that the greatest difficulty arises. Here one must study the rest of the slide very carefully to see if the suspected spot is not composed of the same cells as those about it, with only some slight variations, and the finer points in nucleocytoplasmic arrangement, multinucleation, presence of mitotic figures, etc., must be called upon to make the decision. The presence of fat droplets (vacuolization) is not a helpful finding, since mesothelial cells in long-standing effusions contain them (Fig. 6).

Rather more difficult slides to interpret are those in which the fluid has clotted before reaching the laboratory. In this case the slide consists of a coiled mass of coagulum enclosing scattered cells of many types. It occasionally happens that a picture is presented not unlike a fragment of papillary tumor (Fig. 7). Mistakes are avoided by the recognition of many such coiled forms without cellular elements and the careful study of individual cells.

Another picture occasionally seen is a dense mass of cells with no coagulum separating them (Fig. 8). Here one can find no aberrant cells, since they are all alike. All that one can do here is to compare them (mentally) with cells known to occur in body fluids. If they are different in size, shape and staining properties from the former, if they contain mitotic figures, if they are separate from each other, not forming sheets, and have multinuclear forms, they are probably tumor cells. If, on the other hand, they are similar in size, shape, and staining characteristics to cells ordinarily found in fluids, if they show no mitoses, and if they occur in sheets like mesothelium, one should not report them as tumor cells. These are the cases which, in our series, we have to report as errors (Figs. 6 and 7). They will be discussed at greater length later on.

To repeat, the criteria we have found most valuable are:

1. Fragments of tissue with definite arrangement of cells and stroma, such as glandular acini.

2. Multiple groups of large, deep-staining cells, giving the slide a mottled appearance.

3. Finer cellular changes such as extreme irregularity of cell outline, eccentricity of nucleus, extremely large size of nucleus, multinucleation and typical or atypical mitotic figures.

Analysis of Cases Reported Positive Verified by Subsequent Examination of Tissue (34 Cases). All but 2 of these 34 cases showed sections which were very easy to interpret. Sixteen contained either fragments of tissue or glandular acini in great abundance. The mottled appearance from scattered clumps of large deep-staining cells gave the diagnosis in 16 more. The remaining 2 showed solid

masses of cells, all with the same characteristics, but unlike any cells we have been led to expect in exudates and transudates. The nuclei of the cells in both of these cases showed frequent mitotic figures and marked hyperchromatism (Fig. 8), and readily warranted the report of "tumor cells present."

Analysis of Cases Reported Positive Disproven by Subsequent Examination of Tissue (5 Cases). Had we known at the time these slides were reported what we know now these mistakes would not have been made. All of these cases had long-standing effusions—4 in the peritoneal cavity from cirrhosis of the liver and 1 in the pleural cavity from chronic cardiac valvular disease. They all presented about the same picture (Figs. 6 and 7), dense masses and sheets of large unevenly stained cells, some with pyknotic and some with pale nuclei, many with vacuolated and otherwise degenerated cytoplasm. Some were multinucleated and some grouped themselves around a fat droplet, forming pseudo-alveoli. There were no mitotic figures in any of these sections, whereas they were abundant in the 2 positive cases previously discussed, so that it would seem that in cases of this type the absence of mitotic figures is an important differential point.

Such errors can be avoided in most instances by the application of the criteria just described, but a few cases will occur in which the most experienced examiner will find it almost impossible to make this decision.

Analysis of Cases Reported Negative and Verified by Subsequent Examination of Tissue (31 Cases). From a review of these sections, one gets an idea of the so-called "normal" fluids. Here one sees well-layered fluids (2 cases) or even admixtures of blood cells and mesothelial cells (16 cases). Seven cases showed a homogeneous protein coagulum enclosing occasional scattered lymphocytes and in 2 (empyema) there were solid masses of polymorphonuclear leukocytes. In this group there were 4 cases of long-standing effusion with areas similar to, but not as confusing as, those described in the previous section. Here were sheets of distorted mesothelial cells in bizarre groupings, but in all 4 one could identify them as mesothelial from the fact that they merged with and were continuous with many "normal"mesothelial cells.

Many of the 31 cases showed fluids overgrown with bacteria (Fig. 9), indicating that the fluid had been standing for some time. Under these circumstances, autolysis takes place and the type of cells cannot be properly evaluated. In every case where this occurred, at least one other examination was made and no value was placed on the slide containing bacterial colonies. It is well to remark here that if a fluid is to stand longer than twenty-four hours before being examined it should be layered with toluol to prevent bacterial growth.

Mitotic figures were not found in any section of the 31 cases and

it is doubtful if this phenomenon occurs in cells which find their way into body fluids unless coming from a malignant source. This is in agreement with the findings of Warren and renders Dock's observation absolutely unique.

Analysis of Cases Reported Negative and Disproven by Subsequent Examination of Tissue (43 Cases). In analyzing this group of cases two questions had to be answered:

1. Can tumor cells reasonably be expected to be present in these fluids?

2. Are tumor cells present in some of these fluids having been previously overlooked by the eye of the examiner?

In answer to the first question it can be stated that in 12 out of the 43 cases one could hardly expect the fluid examined to contain cells from the type of tumor found at autopsy. For instance there were:

Two cases of primary carcinoma of the lung in which a single specimen of sputum was examined.

Three cases of primary carcinoma of the stomach in which an unselected specimen of gastric contents was examined.

One case of primary carcinoma of the gall bladder in which a single specimen of gastric contents was examined.

Three cases of primary carcinoma of the kidney in which a single specimen of urine was examined.

Three cases of hypernephroma in which a single specimen of urine was examined.

All of these cases have to do with single examinations of small amounts of special fluids which rarely yield fragments of tissue even upon repeated examination. Intrapulmonary tumors, unless originating in a bronchus, do not yield particles in the sputum, and the digestive properties of gastric juice usually render small shreds of tumor tissue unrecognizable. Obviously, gastric contents cannot be expected to contain tissue from a carcinoma of the gall bladder. As far as the urine specimens are concerned, the amount sent to the laboratory (from 30 to 50 cc.) represents so small a fraction of the daily output, that the probability of finding tumor cells is very slight (of the order of one chance in fifty). Also, the technical difficulties encountered in embedding and cutting the minute amount of centrifugate obtained from urine renders the examination of this fluid of doubtful value.

However, even excluding these 12 cases, there were 16 cases of intrathoracic neoplasm and 12 cases of intra-abdominal neoplasm in which tumor cells could reasonably be expected in the pleural and abdominal fluids respectively, since the respective tumors were shown on autopsy to have invaded the pleura or peritoneum. In a case of spongioblastoma involving the ventricles, the cerebrospinal fluid might have shown tumor cells. Similarly, in a case of cystic glioma of the cerebellum, aspiration of the cyst should also

have revealed tumor cells. The quantity of fluid obtained in the latter 2 instances (only a few cubic centimeters) might explain the failure to find tumor cells in these cases.

Needless to say, all the slides from the 28 cases of intrathoracic and intra-abdominal neoplasms were carefully re-examined and fragments of tissue or clumps of cells were found in 5 instances. In 3 other cases, aberrant cells were found warranting a suggestive report. To be certain that we were not indulging in wish-fulfillment we had all the slides reviewed by an impartial observer* of wide experience who in every case substantiated our findings. Of these 8 cases, 4 were pleural and 4 ascitic fluids. The type of tumor found at autopsy was some type of carcinoma in 7 cases and a sarcoma of the pleura in the eighth.

In the remaining 20 instances, the most careful search failed to reveal any cells which one could label neoplastic. None of them had more than three examinations and 9 had only a single one. Here one can only conclude that the particular sample of fluid sent over did not contain any tumor cells and that if the examination had been repeated several times they might have been found.

Disregarding those cases where cells could not have been expected to be found, and correcting the list of positive cases to include the number obtained above, we have instead of an accuracy of 87 per cent one of 90 per cent when we make a positive report. Conversely, the negative report carries with it only 47 per cent of accuracy which is in keeping with any negative report in any type of examination. (Seecof, analyzing positive and negative cases together found a combined accuracy of 70 per cent.)

In combining both series we can conclude by saying that there were 77 cases in which some fluid was examined for tumor cells and the patient subsequently shown to have a tumor. Of these 77, tumor cells were found in the fluid in 42 instances, or 54 per cent. *Therefore, of all patients with malignant tumors, who develop effusions of any kind, one can expect to find tumor cells in a sample of that fluid in a little more than half.*

Frequency of Conformity between Tumor Cells and Primary Tumor. It has often been asked whether the cells in a pleural or abdominal fluid resemble those of the primary tumor, or lose their original characteristics, after being in fluid for a certain length of time.

In an attempt to throw some light on this subject, I compared the tumor cells in the respective fluid with the primary tumor where such sections were available. This could be done in 17 cases and showed perfect conformity in 14 instances (Figs. 10, 11, 12 and 13), only fair conformity in 2 and no conformity at all in 1. This case was one in which the diagnosis had been made on a very few highly abnormal cells which did not at all resemble the rather orderly cells

* I wish to take this opportunity of thanking Dr. Paul W. Aschner for his kindness in rendering me this valuable service.

of the papillary adenocarcinoma of the ovary discovered at operation. The actual type of tumor could be determined in 12 out of the 17 cases, from the presence of characteristic fragments of tumor tissue.

The diagnosis of adenocarcinoma was justified in 7 instances; of colloid adenocarcinoma in 1; of melanocarcinoma in 1; of hypernephroma in 1; of alveolar carcinoma of the lung in 1; of carcinoma of the bladder in 1.

Frequency of Recognition of Epithelial or Connective-tissue Origin of Tumor Cells. Of the 42 cases in which tumor cells were found in the respective effusions, subsequent examination of tissue showed that 33 were carcinomas, 5 were sarcomas and 4 were malignant tumors of unknown origin.

Conversely in 35 cases in which tumor cells were not found in the effusions, but subsequent autopsy revealed the presence of a tumor, 22 were carcinomas, 10 were sarcomas and 3 were malignant tumors of unknown origin. Stated in other terms: of 55 cases of carcinoma, cells were found in the respective effusion in 33 instances, or 60 per cent, while in 15 cases of sarcoma, cells were found in the effusion in only 5 instances, or 33 per cent.

The greatest number of tumors identified through cells in body fluids is thus seen to be of epithelial origin, and from the previous section it is clear that in a fair percentage of these the actual type of tumor can be determined. This is obviously due to the large number of adenocarcinomas encountered.

Sarcomas were encountered with only one-fourth the frequency of epithelial tumors and recognized in effusions with only one-half the frequency. The exact type of neoplasm could be stated from the cells in the fluid in only 2 cases. It was possible in 1 instance in our series to suspect the presence of intra-abdominal lymphosarcoma from the striking similarity of the cells in the abdominal fluid with those of a lymph node the seat of lymphosarcoma (Fig. 8); and, in another instance, the presence of several fragments of tumor tissue composed of densely packed spindle cells in a pericardial fluid suggested the presence of a spindle-cell sarcoma. This patient had a sarcoma of the epicardium on autopsy. The marked discrepancy between the two classes of tumors, as stated above, can readily be accounted for on the basis of their differences in physical characteristics. Fragments are much more easily dislodged from carcinomas, especially if they are papillary, than from the more dense and circumscribed sarcomas.

Frequency with which Specific Types of Tumor Yielded Cells in Effusions. The following table shows how frequently cells occurred in the effusion from seven common types of tumor. The rarer types of tumor are not listed here because the number dealt with was too small to give any information. The reasons for the failure to find cells in the urine from any of the kidney tumors will be dealt with in the next section.

TABLE V.—COMPARISON OF DIFFERENT TYPES OF TUMORS.

Type of tumor.	Fluid examined.	No. of cases.	Tumor cells found.
Papillary adenocarcinoma of ovary	Ascitic	12	8
Primary carcinoma of lung	Pleural	5	3
Primary carcinoma of bronchus	Pleural	4	2
Carcinoma of the colon	Ascitic	3	3
Lymphosarcoma of small intestine	Ascitic	4	2
Primary carcinoma of liver	Ascitic	3	1
Hypernephroma and carcinoma of kidney	Urine	6	0

Comparison of Different Types of Fluids. Of 35 intra-abdominal neoplasms, 23 or 65 per cent showed tumor cells in the peritoneal fluid whereas in 30 intrathoracic neoplasms only 15 or 50 per cent showed cells in the pleural fluid. This difference can readily be accounted for by the large number of intra-abdominal papillary carcinomas in this series. Also, there were more than twice as many intrathoracic sarcomas as there were intra-abdominal sarcomas, which class of tumors, we have mentioned before, do not readily cast off particles into a surrounding fluid.

Concerning the special fluids such as gastric contents, sputum and urine, our figures are not very extensive but serve to indicate clearly enough that very little can be expected from their examination. Only one of four gastric contents gave evidence of the underlying carcinoma of the stomach and only one sputum in four revealed the presence of cells from the neoplasm of the lung found subsequently. One case of carcinoma of the bladder revealed tumor cells in the urine but no tumor of the kidney revealed itself in this way. We have already pointed out that there is only one chance in fifty of finding tumor cells in urine even if they should be cast off in appreciable quantities in the course of twenty-four hours. The quantity of gastric contents, sputum or urine centrifuged was rarely more than 50 cc. while at least 300 cc. of peritoneal or pleural fluid was represented in its respective centrifugate.

But, disregarding the actual amount of material submitted for examination, the fact that these are constantly moving fluids with little or no chance for prolonged contact with the neoplasm and that they are not physiologic media for the preservation of cell structure, all constitute to make them unfit for cytologic study. Little aid can, therefore, be expected in the future from this type of examination unless the quantity collected be substantially increased and efforts made to render these fluids isotonic. Such an effort has already been begun in the case of gastric contents.

Summary. The centrifuging and embedding technique for examining fluid specimens devised by Dr. F. S. Mandlebaum in 1900 is here redescribed. In some 2000 such examinations made at the Mt. Sinai Hospital a review of the records showed that 113 cases had had a subsequent examination of tissue against which the fluid

examination was checked. When tumor cells were reported as present the report carried with it an accuracy of 90 per cent, whereas when no tumor cells were found, the correct diagnosis was indicated in only 47 per cent. The reasons for the errors encountered are analyzed and some criteria are offered for distinguishing between atypical mesothelial cells and tumor cells. In a series of 77 cases of malignant tumors, cells or fragments of tissue were found in the respective effusions in 42 (54 per cent), in 14 of which marked morphologic similarity was noted in comparing the cells in the fluid with the primary tumor. It was possible to determine the type of the tumor from the character of the cells in the effusion in about one-third of the cases. Whereas 60 per cent of carcinomas showed cells in their respective effusions, only 30 per cent of sarcomas were recognized in this way. In comparing the relative yield of different fluids it was found that peritoneal fluids revealed 65 per cent of intra-abdominal neoplasms, while pleural fluids contained cells of only 50 per cent of intrathoracic neoplasms. Sputum, gastric contents and urine contained tumor cells in only a very small percentage of cases.

Conclusions. 1. The examination of pleural and peritoneal fluids for tumor cells is valuable as a routine laboratory procedure.

2. The positive report should carry with it a high degree of accuracy.

3. The negative report should be considered in the same light as a negative report in any other laboratory method.

4. Atypical mesothelial cells in long-standing effusions provide a source of error to the most experienced examiner.

5. Of all cases of malignant tumors which develop effusions, one can expect to find cells or fragments of tissue in the effusion, in a little more than half.

6. The type of tumor can be determined from the character of the cells in the effusion in about one-third of the cases.

7. There is twice the likelihood of detecting a carcinoma from examination of an effusion, as there is of detecting a sarcoma.

8. The examination of sputum, gastric contents and urine for tumor cells is of little value.

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A CONSIDERATION OF BODY RESISTANCE TO NEOPLASIA;

With Report of a Case of Carcinoma of the Cervix of Long Duration and with Distant Metastases.

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Epidermoid carcinoma of the cervix ordinarily pursues such a typical and prescribed course from the pathologic point of view that the influence which the various factors of body defense exert, and the alterations which the different methods of treatment produce upon the neoplasm's course and behavior, may be fairly

accurately evaluated. The duration of the disease depends largely upon the activity of the body defense mechanism to neoplasia, the type of neoplasm both histologically and clinically, the age of the patient, and the degree of extension of the neoplasm when treatment is first instituted. A consideration of all of these factors permits of a fairly dependable prognosis in the majority of cases, and, in retrospect, often explains the peculiarities in behavior of individual cases.

Fortunately, epidermoid carcinoma of the cervix remains localized. In rare instances only does visceral or distant metastasis occur. From the gross point of view, Kimbrough and Norris[1] recognize two main groups—the papillary, "cauliflower," or everting type, and the infiltrating type. Each form of the disease relatively early in its course begins spreading upward and outward through the lymphatics of the parametrium; these lymphatics constitute the first barrier to the natural progress of the disease. Beyond this, the pelvic lymphatics become involved, the ureters are soon encroached upon, and, in the majority of cases, as Ewing[2] has pointed out, termination occurs through uremia from occlusion of the ureters. As the disease progresses the neighboring structures, particularly the bladder, rectum and vaginal wall frequently become infiltrated from direct extension of the growth.

Surgery and radiotherapy have, in the past, according to available statistics, yielded practically the same end results, and the ultimate mortality has remained high, approaching 90 per cent. It is our belief that this has been partly due to the employment of the same routine treatment procedure in each instance for all types of cervical cancers, with little regard for the factors above mentioned. Radical surgical procedure has apparently reached its high point of efficiency in dealing with cervical cancer, and leaves little to be hoped for in this line of attack; radium and deep Roentgen ray therapy, properly and scientifically employed, have proved very efficacious in both arresting and eradicating cancer of the cervix, and, as pioneer agents, relatively speaking, promise much in the further development and extension of their usefulness in combating malignant disease of this type.

As the proper information regarding cancer is disseminated among the laity, cervical and other types of malignancy will be seen in earlier stages, and as treatment is directed according to the guide factors determined in each individual case, we firmly believe that the mortality percentage will eventually be materially reduced.

The following case of epidermoid carcinoma of the cervix is of interest clinically because of its unusual course and duration, and pathologically because of its method of termination. It is placed on record in the hope that through an analysis of the behavior of atypical as well as typical cases of malignancy further knowledge regarding the effects of the different methods of treatment, particularly in augmenting the rôle played by the host's natural resistance to neoplasia, may be ultimately obtained.

Case Report. I. A., a colored woman, aged sixty-three years, entered the Philadelphia General Hospital, May 9, 1926, complaining of "stomach trouble."

In 1918, she was treated at the Roosevelt Hospital, N. Y., for epidermoid carcinoma of the cervix, cauliflower type. Radium was implanted in the cervix, and a dosage of 2400 mc. hr. was given. Following this, a panhysterectomy was performed. Since that time, she had been under their observation, and no recurrence was noted.

Her present illness began in November, 1925, with a persistent, irritating cough. In February, 1926, a mass was noted in the epigastrium slightly to the left of the midline. When first noticed, it was the size of a lemon; this increased in size and subsequently appeared to be as large as an orange. This lump had caused her very little discomfort.

Pain first occurred during March, 1926. It was sharp and stabbing in character, radiating from right to left across the upper abdomen. During the following three months she lost 30 pounds in weight, and her appetite failed. When examined at the Roosevelt Hospital during March, 1926, note was made of the abdominal mass, the liver was enlarged and the spleen was palpable. Roentgen ray study of the chest revealed metastatic nodules in the lungs (Fig. 3). The osseous system was negative.

Our physical examination revealed an emaciated, aged, colored woman weighing about 90 pounds. She did not appear to be acutely ill, but was so weak that she was confined to bed. Her mentality was unimpaired. There was moderate dullness on percussion over the right upper thorax, posteriorly. The breath sounds in this area were distant. Aside from this the pulmonary findings were negative. The cardiovascular system appeared to be normal for her age.

The abdomen was sunken. The liver was just palpable below the costal margin. A firm, nodular mass, apparently fixed to the deep structures, was felt in the left midepigastrium. The scar from the operation in 1918 was noted in the midline of the lower abdomen.

Due to previous irradiation and operation, the vagina was very small, and its mucosa was atrophic. The uterus and adnexa were not present. There was no evidence of pelvic disease or recurrent neoplasm.

The Wassermann reaction was negative and the blood chemistry was within normal limits. The urine was negative, and Roentgen ray plates of chest showed shadows throughout each lung that were interpreted as representing metastases.

Four areas anteriorly and four areas posteriorly over the lung fields were mapped out. A series of ten treatments of 15 milliampères each were given anteriorly and posteriorly, alternating, that is, treating the anterior ports one day and posterior ports the next. The factors were three minutes, 5 milliampères, fourteen seconds spark gap, ½ mm. Cu., 2 Al. filtration, 50 cm. S.T.D. 20 cm. field. This treatment was without apparent benefit, and the patient gradually grew weaker and died, on June 25, 1926.

Pathologic Study. The necropsy findings were of unusual interest. There was marked bodily and organic wasting. Each lung was diffusely studded with many firm, rounded, cellular, whitish tumor nodules (Fig. 4), which varied from 2 to 20 mm. in diameter. The liver was enlarged to twice normal size and was largely replaced by neoplastic tissue (Fig. 4). The tumor deposits were similar in appearance to those seen in the lungs. They varied from 3 mm. to 5 cm. in diameter; many of them were confluent. The mass palpable in the epigastrium proved to be a confluent group of tumor nodules in the liver.

There were several small metastatic growths of the same character and appearance in the cortex of the right kidney (Fig. 4). The uterus, tubes and ovaries had been completely removed, and the entire pelvic floor was smoothly covered with peritoneum. Careful search revealed no evidence

FIG. 1.—Low-power photomicrograph (× 90) of biopsy specimen removed in March, 1918. Note heavy lymphocytic infiltration of loose fibroblastic tissue between the invading epidermal processes. Many eosinophils are also present.

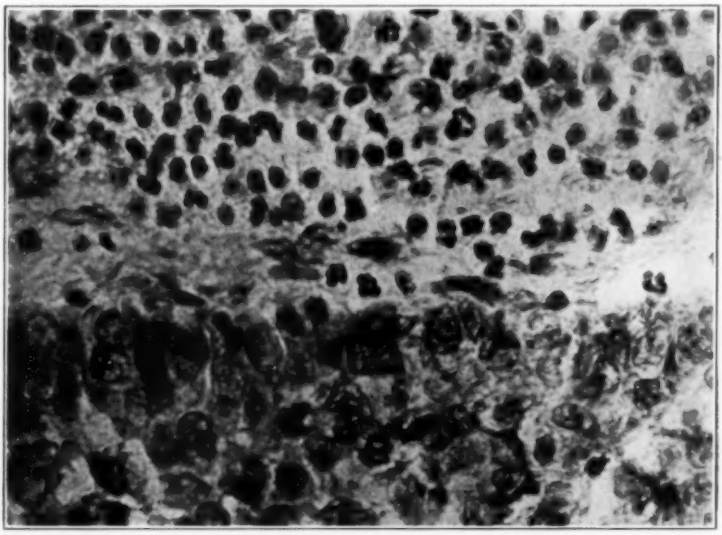


FIG. 2.—Oil-immersion photograph (× 700) of preparation illustrated in Fig. 1, showing invading border of unripe epidermal cells, several of which are undergoing cell division. Many lymphocytes and eosinophils are recognizable beyond this border.

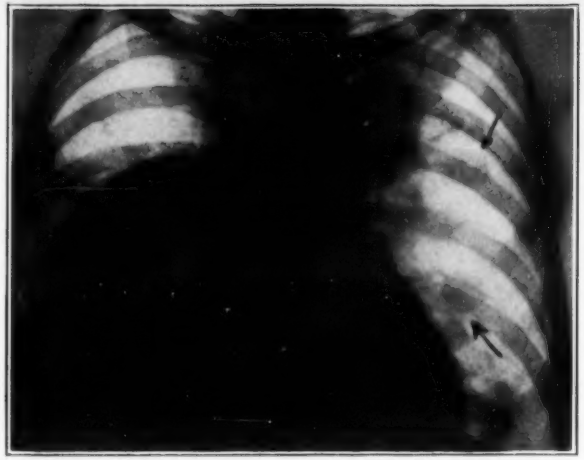
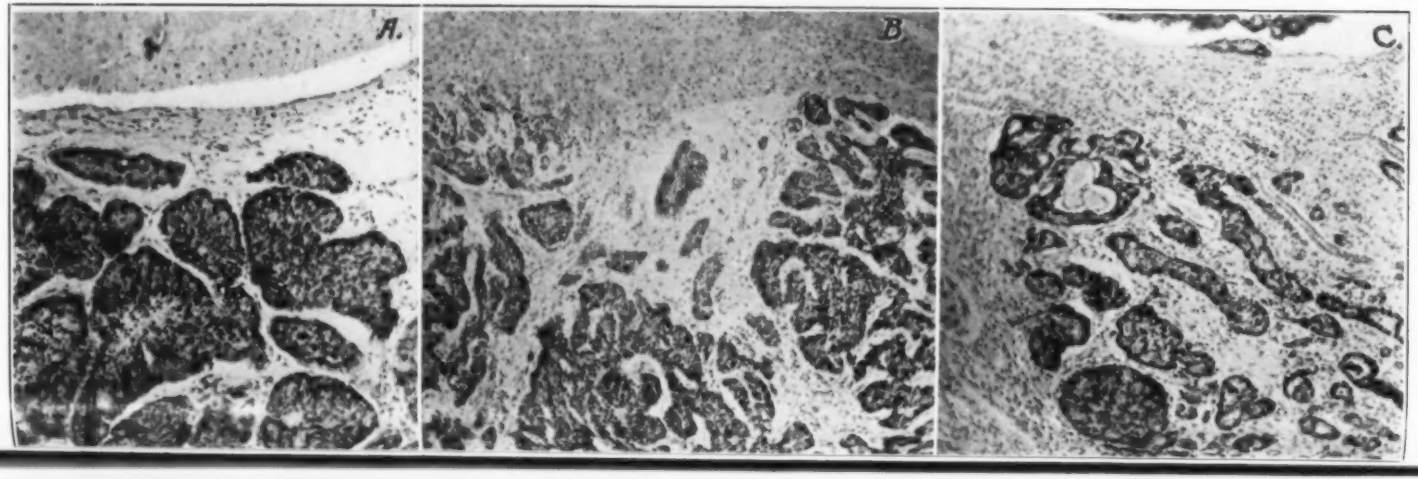


FIG. 3.—Roentgen ray of chest, taken in March, 1926, showing shadows which represent metastases.



of pelvic disease or neoplasm. The gastrointestinal tract was negative throughout, and the remaining gross findings were of no consequence.

The appearance, mode of growth, and general distribution of the tumor nodules in the involved organs were those of metastatic carcinoma, and as thorough examination of each organ revealed no primary neoplasm, the condition was regarded as being secondary to the primary carcinoma of the cervix demonstrated eight years previously.

Histologically, the tumor proved to be a neoplasm composed of relatively undifferentiated or unripe epidermal cells. Sections from the lung, liver, and kidney deposits all gave the same general picture—nests and cords of closely placed, deeply staining cells which were growing invasively by peripheral extension. The border of each nest was composed of cells morphologically similar to basal cells; the inner cells corresponded to the transitional type. Prickles and pearly bodies were not demonstrable, and mitotic figures were numerous.

The recurrent tumor, when compared with the primary neoplasm, sections of which were made in March, 1918, at the Roosevelt Hospital, New York, showed only minor differences in the morphology and appearance of the cancer cells. The cells of the original tumor (Fig. 1) appeared slightly more differentiated and more mature than those of the recurrent neoplasm, but in each instance the tumor was graded a No. 3, according to Broder's[3] classification, or classified under the "transitional-cell type" designation according to the method of Martzloff.[4]

Study of the original sections, however, revealed that there was striking body resistance to the cancerous growth. There was demonstrable a considerable amount of loose fibroblastic tissue between the invading epithelial processes, the ratio of neoplastic tissue to fibrous tissue being approximately 6 to 4. This tissue was heavily infiltrated with mononuclear cells, the majority of which were lymphocytes. These were in such numbers as to give a picture resembling lymphoid tissue in places (Fig. 1). Eosinophils predominated among the polymorphonuclear cells that were present. The average number per high-power field was 20 to 30, and as many as a hundred were counted in several fields (Fig. 2).

Comment. This patient lived for more than eight years after an epidermoid carcinoma of the cervix had been diagnosed and locally eradicated by the combined radium and surgical method. The ultimate fatal termination, we feel, may be ascribed to insufficient and nonenduring resistance to neoplasia, since the absence of local recurrence throughout the tenure of the neoplasm is an indication of the efficacy of the treatment employed, as far as the primary growth was concerned. In retrospect, the activity of the defense factors in this case throw considerable light upon the course and behavior of the disease.

The cancer was composed chiefly of transitional or only partly differentiated squamous epithelial cells, the group into which the great majority of cervical cancers fall. Paralleling the law of normal cell growth, cells of this type exhibit more rapid growth tendencies than those that correspond morphologically to the more mature cells of the superficial layers of the epidermis, and possess less growth impulse than the wholly undifferentiated or basal-like cells lower down. The vulnerability of a cell to destructive physical agents varies inversely with its degree of differentiation, so that the seeming handicap of rapid rate of growth common to

those tumors of undifferentiated or partly differentiated cell type, may actually be converted into a relatively favorable prognosis by reason of the sensitiveness of the neoplastic cells to the destructive agent employed in treatment. The cell of the transitional type may be considered definitely "radiosensitive," and we believe, the radium dosage which our patient received actually killed the majority of the cancer cells early in the course of the disease.

The activity of the natural factors of body defense played a prominent rôle in limiting the progress of this neoplasm. Evidence of body resistance to neoplasia is noted in the proliferation of the fibroblastic tissue about the invading tumor which is interpreted as an attempt to obstruct the progress of the tumor's growth. The accumulation of large numbers of mononuclear cells, chiefly of the lymphocytic type, constitutes a defense measure frequently employed by the host in combating chronic, progressive disease of any type.

We regard the gathering of many eosinophils locally as further evidence of body resistance to neoplasia. Very little is known about the eosinophil, or its function, but in studying a series of cases of carcinoma of the cervix, we have been impressed with the observation that, in those instances where local eosinophilia has obtained, the patient has exhibited a greater resistance to the disease, has responded better to treatment and has lived longer than when eosinophilia was absent. We regard the presence of the eosinophil as a good omen in carcinoma of the cervix, and the greater their number the more favorable is the prognosis. Schoch's[5] recent study of 417 radiologically treated cases of carcinoma of the cervix showed that in the 40 cases with eosinophilia the proportion of five-year cures was 45 per cent while in the 367 cases without eosinophilia, it was only 10 per cent. Pavlovsky and Widakowich[6] believe that eosinophils have protective properties against cancer invasion.

From the clinical point of view, the age of the patient, the duration of symptoms, the stage at which treatment is first instituted and the gross form of the cancer are indices to prognosis that are further helpful in analyzing the relationship of neoplasm to host. Normally, growth impulse tends to wane progressively as the body ages, and, in neoplasia, as a general rule, the older the patient is the slower does the neoplasm grow, the later does it metastasize, and the more mature is its cell-type likely to be. The duration of signs and symptoms, accurately observed, usually parallels closely the degree of involvement of the cervix when the patient's age, and the cell-type of the neoplasm are taken into consideration. Kimbrough and Norris'[1] study shows that the papillary or everting type of cancer responds better to proper treatment, and permits of a more favorable prognosis than the infiltrating type.

The rational treatment of cervical carcinoma should have a dual objective: (1) To eradicate the disease locally; (2) to strengthen or build upon the patient's natural resistance to neoplasia. This,

we feel, may be best accomplished by directing treatment according to the degree of cell differentiation of the tumor, a determination readily made by biopsy study. Those neoplasms composed chiefly of wholly undifferentiated or partly differentiated cells, while possessing rapid-growth tendencies by virtue of their unripeness, are vulnerable and "radiosensitive," and, we feel, are more effectively combated by massive heavy radiation at the initial treatment.

The response of the neoplasm to such treatment determines whether or not repeated applications of radium are indicated. In a favorable response, local healing ordinarily occurs in six to eight weeks after irradiation; complete healing within three months after treatment is the generally accepted criterion of a satisfactory immediate response to irradiation. As regards age Kimbrough and Norris[1] found their best response to irradiation in patients between the ages of forty-five to fifty-five.

In those instances where the predominating cells are differentiated or mature and correspondingly possess slower growth impulse and are more resistant to irradiation, we would suggest repeated applications of radium in smaller dosage over an extended period of time. Such procedure seems rational on the basis that ripe, resistant cells may be crippled by repeated injury, and that cells undergoing mitotic division are especially easily destroyed by radium, and, dividing at irregular intervals, are more likely to be caught by this plan. In this manner growth of the tumor can be greatly retarded, even if the neoplasm itself cannot be wholly eradicated.

In either instance, irradiation as is well known, promotes local fibrosis, and we have indicated that the proliferation of fibroblastic tissue is an important factor in arresting the progress of the neoplasm. It is probable also that irradiation promotes the production of eosinophils. In this sense, then, radiotherapy may be thought of as actually augmenting or strengthening the body's natural resistance to neoplasia.

The opportunities for the surgical removal of cervical cancers are relatively few, since in our opinion, in only those instances where the tumor is small, young and definitely confined to the cervix is radical surgical procedure justified, and then only after adequate irradiation. Unfortunately, the majority of cases when first seen are found to be practically inoperable because of involvement of neighboring tissues or organs. We feel that it is practically impossible for any surgeon to remove all of the tumor tissue in such cases, and even in borderline cases we regard the attempt to do so as greatly jeopardizing the patient's chance for a cure. Not only does such procedure fail in accomplishing the double objective desired but it actually interferes with and curtails the progress and activity of the natural body defense factors, thus handicapping the subsequent last resort, radiotherapeutic endeavors that too often are of no avail. The use of the actual cautery, on the other hand, in amputating the cervix in the papillary or "cauliflower" type and

in eradicating much of the neoplasm in the infiltrating type of cervical carcinoma, largely for facilitating the more accurate and efficient placing of radium, has given excellent results in our experience.

It is our feeling that radiotherapy, scientifically and properly employed, offers a greater likelihood of a cure than does surgery and comes nearer accomplishing the double purpose of treatment when used without surgery as an adjunct.

Summary. 1. A case of epidermoid carcinoma of the cervix living over eight years after eradication of the primary lesion by the combined radium and surgical method and terminating by distant metastasis is reported.

2. The natural resistance of the body to neoplasia is considered. Fibroblastic tissue proliferation and lymphocytic infiltration about the invading tumor tend to limit and prevent the progress of the neoplasm.

3. The eosinophil is a good omen in carcinoma of the cervix, and in addition to being an important defense factor is a valuable index to prognosis.

4. The histologic type of the tumor cells is a reliable criterion upon which to base prognosis from the pathologic point of view and should be used as a guide for the plan of treatment employed. The age of the patient, the duration of signs and symptoms, the gross form of the neoplasm and its degree of extension are important clinical prognostic factors.

5. Treatment of carcinoma of the cervix should have as its objective a double purpose: (*a*) To eradicate the disease locally; (*b*) to augment and build upon the natural factors of body defense to neoplasia.

6. Radiotherapy approaches this dual objective more closely than does surgery. The cautery is an important aid in the technique of radium placing.

NOTE.—We wish to acknowledge with grateful appreciation the data concerning the early history of this case and histologic sections of the primary tumor which were generously furnished us by the Gynecologic Staff of the Roosevelt Hospital, New York.

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SOME UNUSUAL AND ATYPICAL INTRATHORACIC CONDITIONS.*

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Introduction. Intrathoracic diseases often offer grave diagnostic difficulties. At times this is due to the occurrence of an unusual clinical entity, but again, it may be due to an atypical manifestation of some common disease. For the past two years, we have collected these experiences. Some of our patients were seen in the course of our study of lobar pneumonia.[1] Others were met with during the routine medical service or in consultation on the surgical service.

I. Intrathoracic Accidents. *A. Acute Spontaneous Pneumothorax.* On four occasions we have encountered an acute spontaneous pneumothorax occurring in otherwise healthy individuals. In two instances (No. 88 and No. 241), the accidents occurred following strain; that is, handball in the first instance, and running upstairs after a heavy meal in the second instance. The diagnosis in both patients was perfectly apparent from the physical examination and was confirmed by a radiograph (Fig. 1). When the air had been aspirated, in neither instance was there any evidence of tuberculosis and both patients made a complete and uneventful recovery.

Slightly more complicated was the diagnosis in patient No. 159. This man had been admitted to the hospital suffering from grippe. After one day of fever, he became afebrile (Chart I). Late one night, while lying in bed, he suddenly developed a pain in his chest and a temperature of 105.6° F. A blood count revealed a marked leukocytosis, and it was at first suspected that he had developed an acute pneumonia. The physical signs, however, were suggestive of pneumothorax, and on aspiration, a positive pressure was made out. Radiographic examination the next morning showed a residual cap of air at the left apex (Fig. 2). The next day his temperature was normal, he made a complete recovery, and showed no evidence of tuberculosis (Fig. 3).

A somewhat similar accident occurred in a colored man (No. 213), following an appendectomy for gangrenous appendix. On the

* A number of patients were seen on the surgical service of the hospital, and some of the medical patients were studied through the courtesy of Drs. B. S. Oppenheimer, G. Baehr and A. A. Epstein. The radiographs are reproduced through the courtesy of Dr. Jaches, director of the radiographic department. The interpretations were made by Dr. H. Wessler. The pathological examinations were furnished us by Dr. Klemperer. The bronchoscopic examinations were performed by Dr. Sidney Yankauer and the various members of his staff. To all of our colleagues we are indebted for their courtesy and coöperation.

second postoperative day, he developed what appeared to be a postoperative pneumonitis. For four days he had fever, and coughed up some stinking sputum. Three days later he had sharp pain in the chest and developed clear-cut signs of partial pneumothorax. This was confirmed by a radiograph. Within a few days the chest cleared completely.

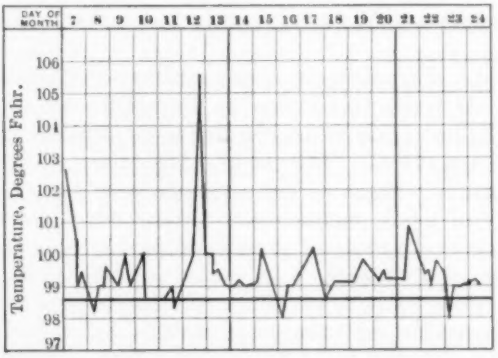

CHART I.—Temperature chart of patient No. 159, who came in at the end of an attack of grippe, and five days later developed an acute spontaneous pneumothorax, with a temperature elevation of 105.6° F.

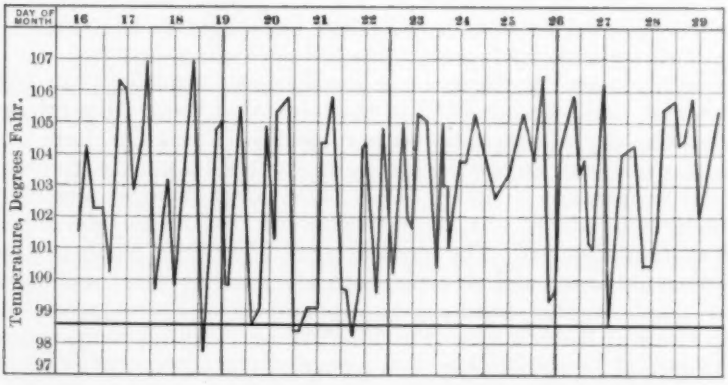

CHART II.—Patient No. 31. A portion of the temperature chart of the boy with an intrathoracic suppuration following perforation of the esophagus by a bone from chopped meat.

B. Perforating Lesions of the Esophagus. Perforating lesions of the esophagus may give rise to bizarre intrathoracic complications and signs. A boy, aged thirteen years (No. 31), after having eaten some chopped meat five days before admission, felt an immediate pain in his chest. For four days he had pain in the right chest, dyspnea, cough, fever and sweating. The day before admission he became nauseated and chilled. He was acutely ill when

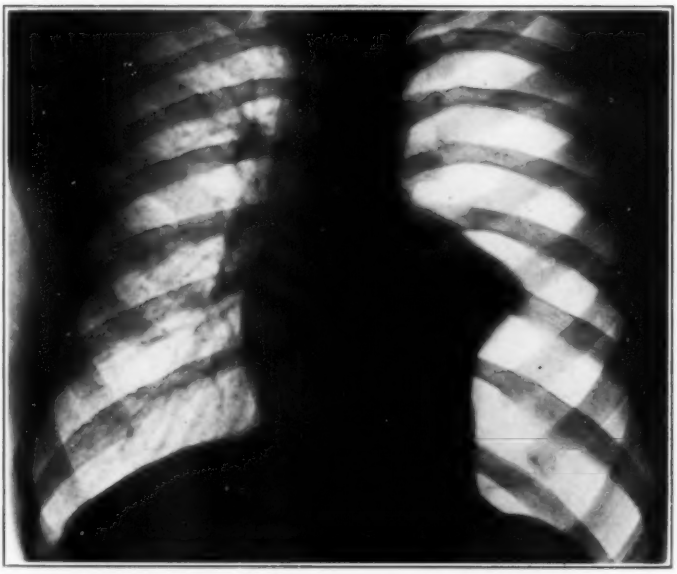

FIG. 1.—Patient No. 241. Acute spontaneous left-sided pneumothorax occurring in normal lungs following strain.

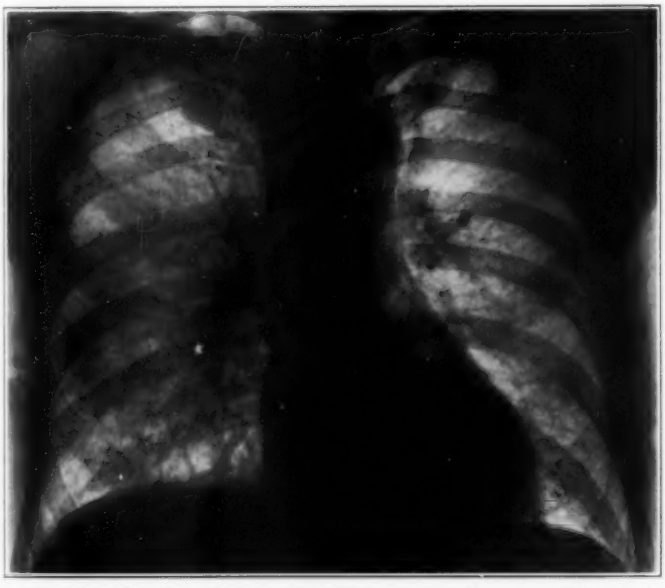

FIG. 2.—Patient No. 159. Acute spontaneous pneumothorax occurring during the course of grippe.

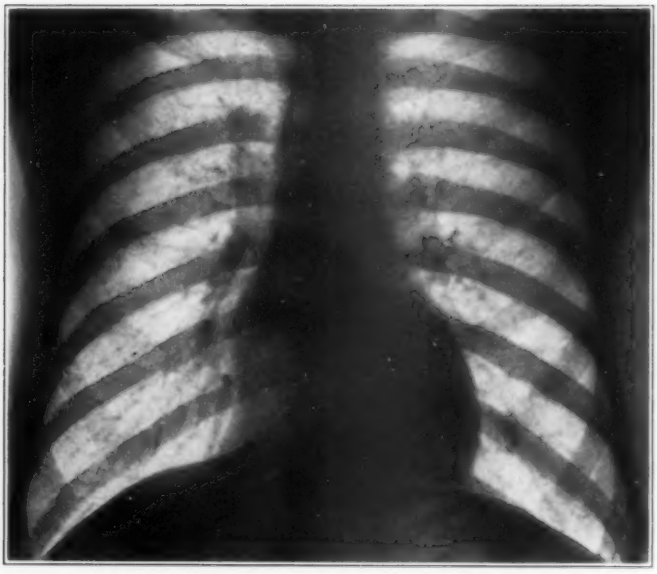

FIG. 3.—Same patient as Fig. 2, showing normal lungs after absorption of air

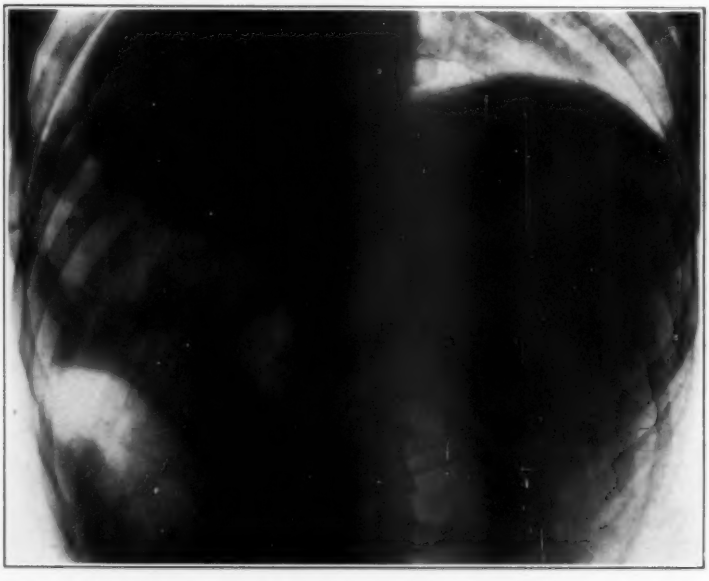

FIG. 5.—Patient No. 261. Radiograph of the lower ribs for fracture, showing the radiability of both lower lobes preceding the pulmonary collapse.

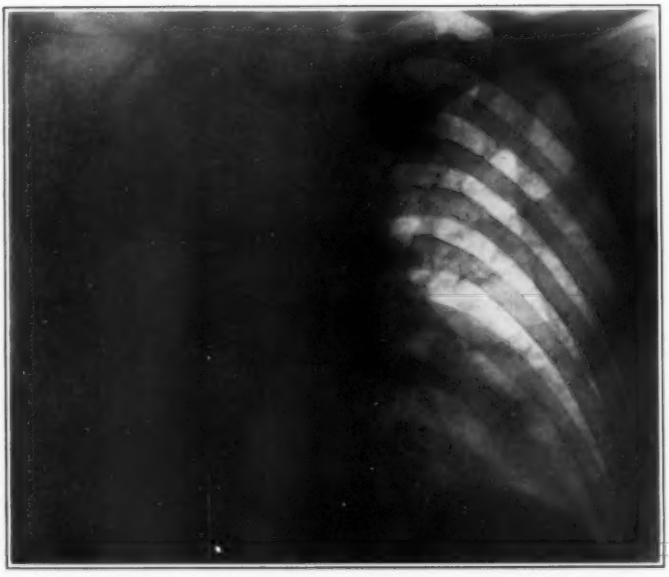

FIG. 6.—Same patient, showing complete collapse of the left lung ten days after fracture of the right lower ribs without penetration.

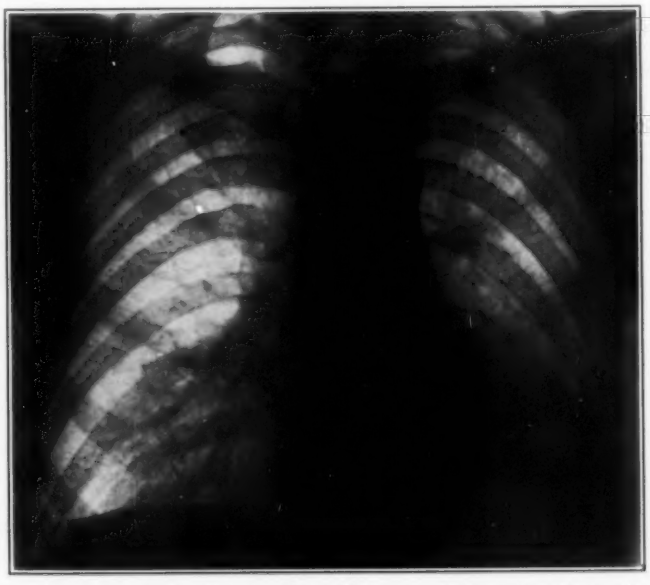

FIG. 7.—Same patient, showing aëration of left upper lobe and residual collapse of left lower lobe.

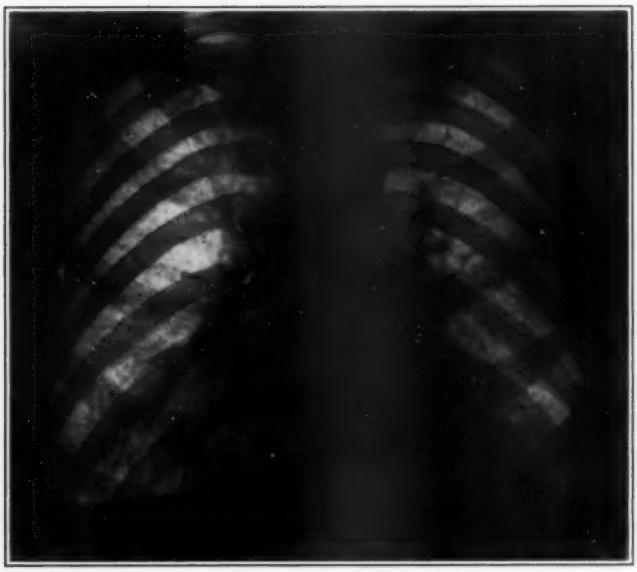

FIG. 8.—Same patient, showing relatively complete recovery.

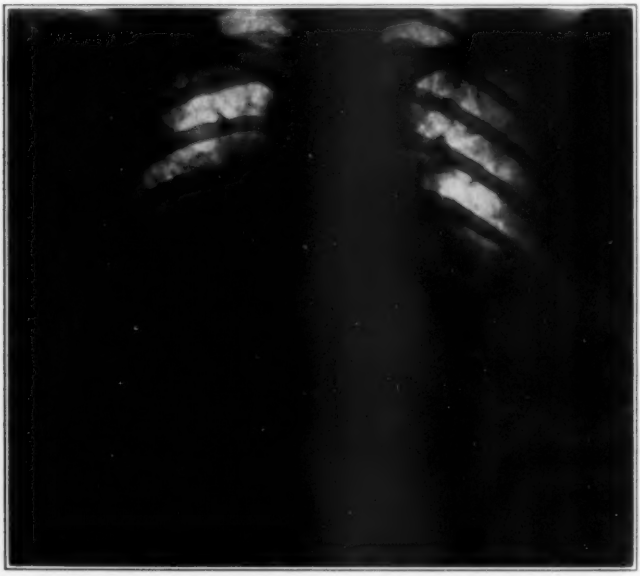

FIG. 9.—Patient No. 49. Collapse of both lower lobes thirty-six hours after appendectomy.

FIG. 10.—Post-tonsillectomy lung abscess in patient No. 119.

FIG. 11.—Same patient three months later.

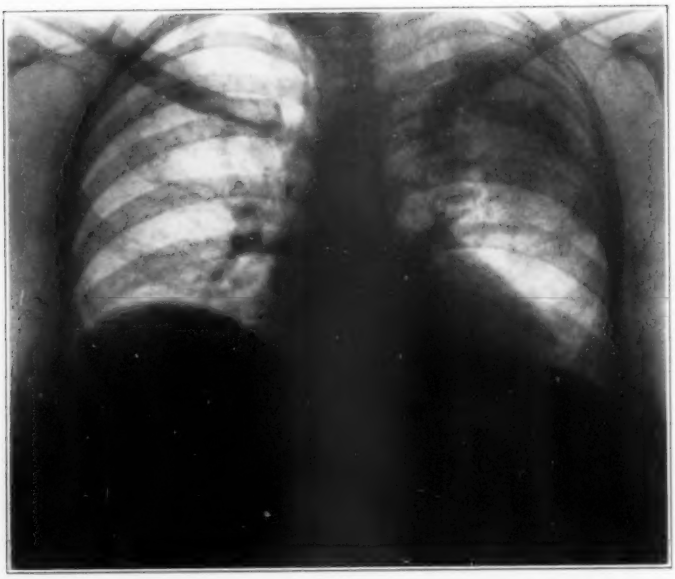

FIG. 12.—Patient No. 229. Acute lobar pneumonia occurring twenty-four hours after tonsillectomy under local anesthesia.

FIG. 13.—Patient No. 175. Activation of pulmonary tuberculosis following tonsillectomy under general anesthesia.

FIG. 14.—Same patient five weeks later.

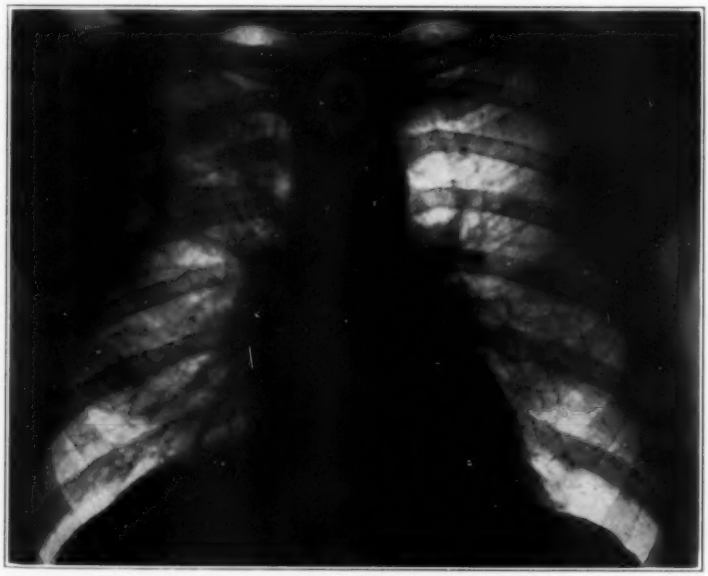

FIG. 15.—Patient No 273. Lung abscess showing fluid level This apparently followed extensive dental work.

FIG. 16.—Patient No. 169. A boy aged nineteen years with pulmonary tuberculosis, who had hemoptyses which came from a walnut shell in the bronchus.

FIG. 17.—Patient No. 239. Persistent bronchopneumonia probably due to infection of the lung by the rheumatic virus.

FIG. 18.—Patient No. 177, a probable two-day pneumonia.

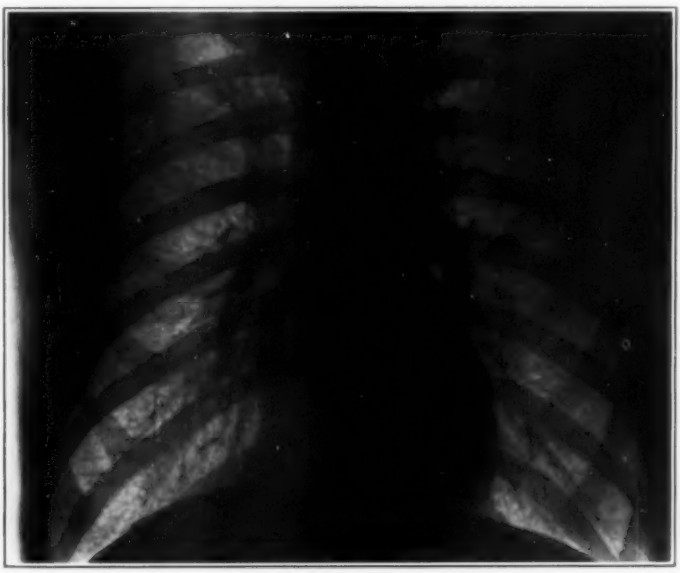

FIG. 19.—Patient No. 232. Resolving pneumonia.

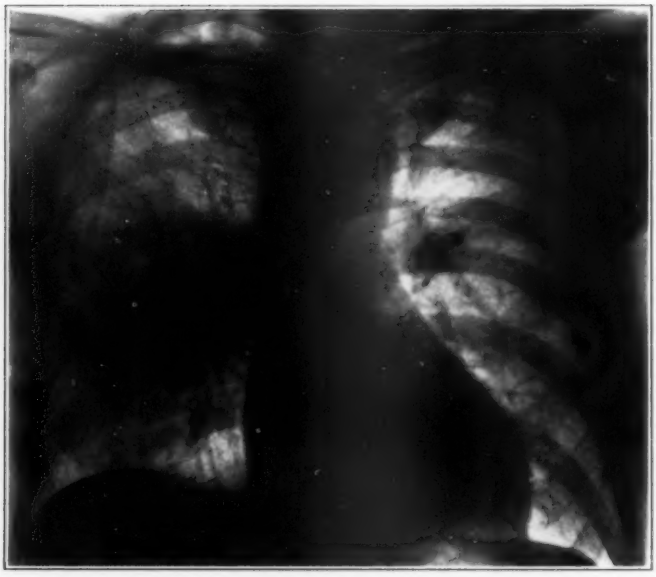

FIG. 20.—Return of pathologic process in Fig. 20. At autopsy this was found due to an infarction of the previously consolidated area.

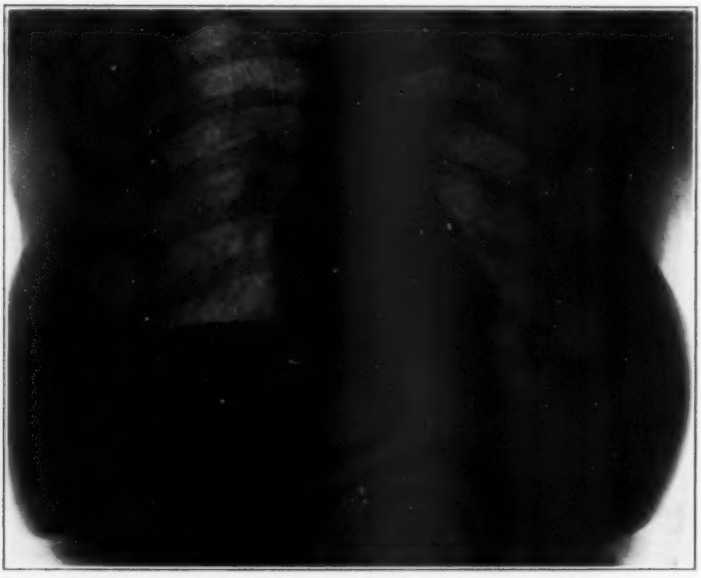

FIG. 21.—Patient No. 242. Miliary tuberculosis in a girl without pulmonary symptoms.

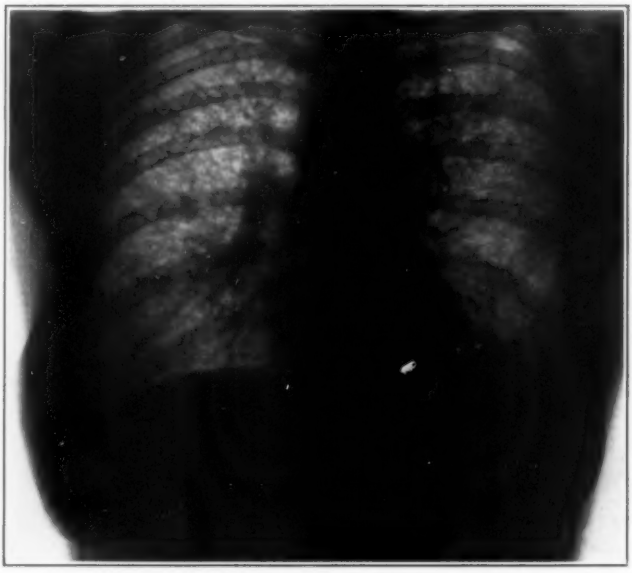

FIG. 22.—Patient No. 243. Subacute miliary tuberculosis in a woman without pulmonary symptoms or fever.

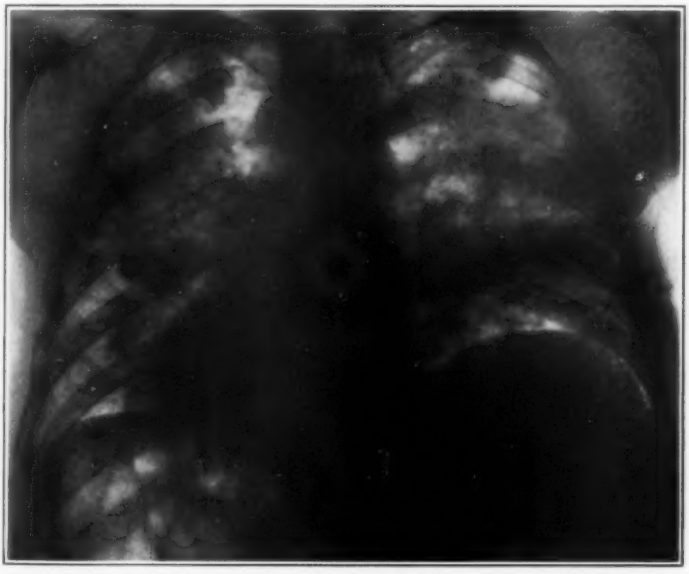

FIG. 23.—Patient No. 251. A man with situs inversus and metastases in the lung seventeen years after the removal of a bladder carcinoma.

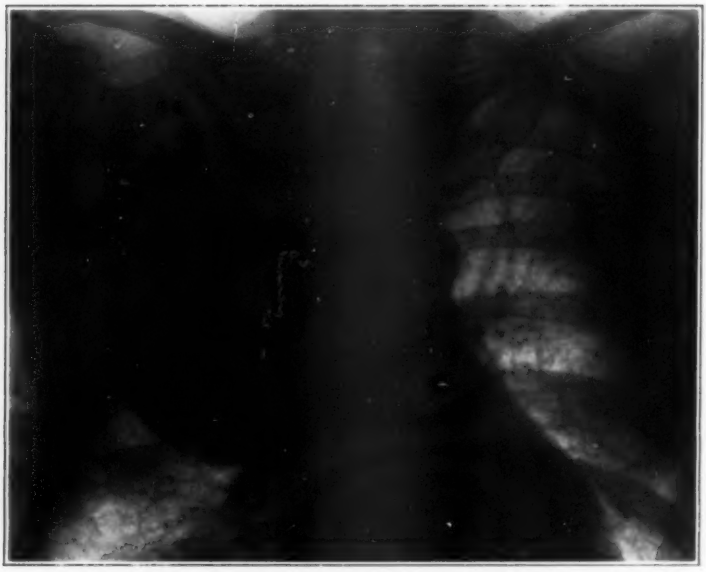

FIG. 24.—Patient No. 50. Neoplasm of the lung.

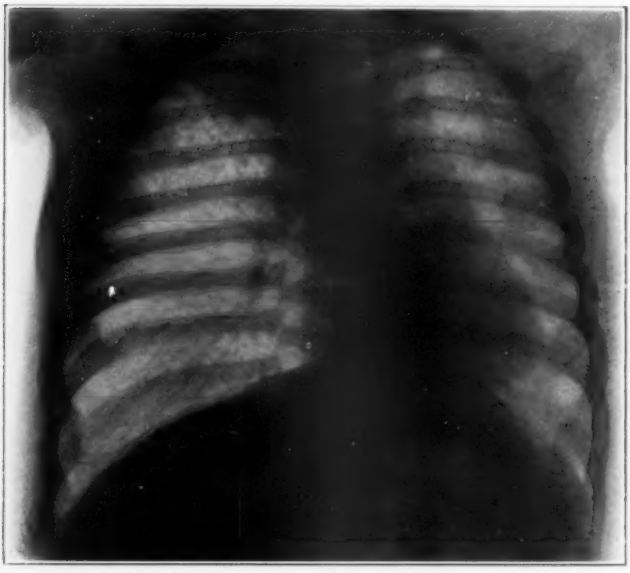

FIG. 25.—A child, aged eighteen months, with atelectasis of the right upper lobe, probably from the pressure of tuberculous glands.

first examined (Chart II), but the only physical signs were diminished breathing over the right lower lobe and some costovertebral tenderness. Endoscopy revealed a perforation in the esophagus, and the boy was operated on in an attempt to evacuate the pus. He died shortly after. At autopsy, there was present in the right pleural cavity about 30 cc. of thick pus. On the surface of the right lung were numerous large and small abscesses. The surrounding lung tissue was markedly edematous. Some of the smaller blood-vessels leading to the abscesses contained small, friable thrombi. The lymph nodes at the hilus of the lung showed a purulent infiltration. The left pleural cavity contained 400 cc. of a light yellowish purulent exudate, and in the left lung were numerous small and large abscess cavities. The esophagus had a punched-out ulcer about ½ cm. in diameter. This was approximately 25 cc. from the

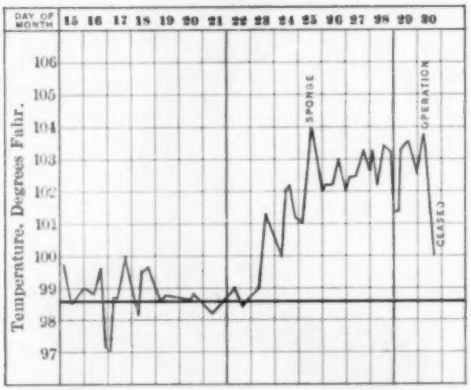

CHART III.—Patient No. 32. Temperature of a man who developed an infected hematoma of the mediastinum from a perforation by a fish bone of the esophagus and aorta.

upper teeth. A portion of the vena azygos major over this ulcerated area contained an adherent thrombus measuring about 2 cm. in length. No foreign body was found, and there was no other thrombosis or purulent infiltration in the remainder of the venous system. From the autopsy findings, a reconstruction of the events could be made. A spicule of bone in the chopped meat had apparently perforated the esophagus and the vena azygos major. An infected thrombus had formed in the wall of the vein, and the lung abscesses were probably from infected emboli.

A very similar accident occurred in a man aged thirty-five years (No. 32), who, after having eaten a meal of fish ten days before admission, developed intense retrosternal pain. On admission, he had a profuse hematemesis and appeared to be acutely ill. He had dullness and diminished breath sounds over the left upper lobe,

and slight extension of the cardiac and mediastinal dullness to the right. On esophagoscopy, a ragged mucosa was seen at 35 cm. Repeated radiographs finally demonstrated a slight increase in the width of the mediastinum and a slight displacement of the lower trachea to the right. The patient was seriously ill (Chart III), and

FIG. 4.—Patient No. 32. Specimen showing perforation of esophagus and aorta by a fish bone resulting in an infected hematoma of the mediastinum.

a posterior mediastinotomy was made. Nothing abnormal was found. Seven hours after operation, he had a hematemesis and died. At autopsy (Fig. 4), "the trachea was pushed markedly to the right and the arch of the aorta to the left by a large mass which was about 8 cm. in diameter. There was a large ragged wound measuring about 2 cm. square on the anterior and left aspect of the esophagus.

Here the mucous membrane was necrotic and friable, and a large mass of bloodclot protruded through this ragged opening. This opening communicated with the above described mass which was situated between the trachea and the arch of the aorta. The mass itself was hollow and filled with friable bloodclot, much of it old and partially decolorized. It presented the appearance of hematoma. At the point in the arch of the aorta, which was immediately contiguous to this hematoma there was found a small perforation of the vessel wall hardly larger than a pinhead. That this was not an artefact, but existed during life, was evidenced by the fact that the intima for a distance of 7 mm. around this perforation was covered by tightly adherent blood-platelet thrombus. Although search was made, no fish bone or other foreign body was discovered in the thoracic cavity. The postmortem findings confirmed the clinical diagnosis of a traumatic injury to the wall of the esophagus just above the level of the bifurcation of the trachea. The penetrating object apparently caused a minute perforation of the arch of the aorta. The slight leakage through this penetration resulted in a large hematoma in the superior mediastinum, which in turn produced pressure upon the wall of the esophagus. Eventually the clot in the hematoma began to break down, whereupon the pressure in the aorta again resulted in a leakage of blood through the small perforation in the aortic wall and death occurred from secondary hemorrhage."

C. Traumatic Effusions. Traumatic effusions may follow injury to the chest wall. Such an accident occurred in a man aged thirty-five years (No. 201), who received a blow on his chest and ten days later was admitted with a nonhemorrhagic pleural effusion. This was aspirated and he made a complete recovery, and showed no evidence of neoplasm or pulmonary disease. This is probably a not infrequent occurrence.

D. Collapse of the Lung following Trauma. A more complicated example of an intrathoracic lesion following external injury is illustrated by a man aged forty-one years (No. 261), who had received a fracture of his left lower ribs in a traffic accident. The fractures were simple and there was no evidence of pulmonary penetration (Fig. 5). Ten days after the accident, the patient went into a state of shock (Chart IV), and showed a massive collapse of the left lung (Fig. 6), which was contralateral to the injury. A film of the chest taken a few days before this, had shown the lungs to be clear. We were dealing, therefore, with a contralateral collapse of the lung occurring ten days after a nonpenetrating fracture of the ribs. Five days after the collapse of the entire lung, the upper lobe opened (Fig. 7), and ten days later the patient was restored to normal and made an uneventful recovery (Fig. 8).

II. Postoperative Complications. Postoperative complications other than the routine postoperative pneumonitis occur not infrequently.

A. Collapse of the Lung. Collapse of the lung is becoming recognized more frequently.[2,3] An instance illustrating this occurred in a girl aged twenty-years (No. 49), who, thirty-six hours after appendectomy, developed typical signs of a massive collapse of both lower lobes (Fig. 9). She made a complete recovery.

B. Postoperative Embolism. The diagnosis of postoperative embolism[4] is made with less certainty than collapse. Frequently the diagnosis is justified, as in the instance of a woman age forty-one years (No. 82). This patient, after an anterior colporrhaphy, developed mild pain in the chest associated with a slight elevation of temperature, though there were no physical signs. Two weeks later there was repetition of the picture. This time the febrile reaction and the pain were more severe. On all occasions radiographs of the chest were normal, and there were no definite physical signs. Two months later, there was a third accident of this type,

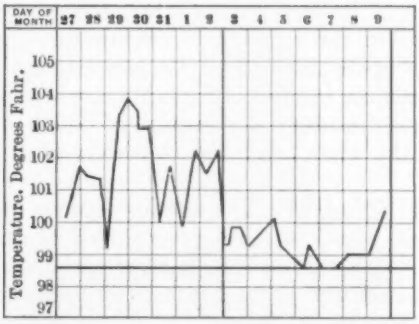

CHART IV.—Patient No. 261. Temperature chart of a man who developed an acute collapse of the left lung ten days after fracture of the right lower ribs.

and a small patch of tubular breathing with some râles was made out. The patient made a complete recovery, and it seemed most likely that we were dealing with multiple embolic phenomena from a thrombophlebitis which was secondary to the operation.

Somewhat more definite than this was the course of a man aged fifty-two years (No. 246), who, following a herniotomy, developed both cerebral and pulmonary symptoms. When he was examined for these complications, it was discovered that he had a mitral stenosis. The signs of both accidents rapidly disappeared. The suspicion was strong that both had been evidences of multiple emboli.

III. Special Pulmonary Complications following Operative Procedures in the Nose and Throat. We have encountered a number of interesting pulmonary complications following bronchoscopy and tonsillectomy.

A. Acute Bronchopneumonia following Bronchoscopy. An acute bronchopneumonia may occur following bronchoscopy. This does not often occur following a diagnostic bronchoscopy, but it does occur not infrequently following lavage. More often it will be experienced in patients who have bronchiectasis rather than lung abscesses. An example of this occurred in a man aged fifty-eight years (No. 183), who had been treated for several months by bronchoscopic lavage for the relief of symptoms due to multiple bronchiectases. He developed a chill and constitutional signs. After a few days, the temperature fell, and he was restored to his previous condition.

A very careful record should be kept of the chest signs of all patients who are treated by bronchoscopy. In this way one can recognize fresh lung signs, whereas otherwise it is often impossible to know which of the signs are old and which are recent.

B. Lung Abscess.[3,6] Lung abscess may follow tonsillectomy. In our experience, this occurs much more commonly after general anesthesia than after local anesthesia. The signs and symptoms usually occur from ten to fourteen days following the operation. A typical instance occurred in a girl aged twenty-four years (No. 119), who, ten days after operation, developed pulmonary symptoms. Two weeks later, she entered the hospital with a very definite cavity containing a fluid level (Fig. 10). On postural drainage and bronchoscopy, she made a complete recovery (Fig. 11). This experience, while not unusual, unfortunately is not the invariable rule. At times these abscesses become chronic, conservative therapy fails, and some type of operative interference becomes necessary.

A most unusual example of the same condition occurred in a young man who had a tonsillectomy under local anesthesia in a doctor's office, and then went home. Two weeks later he was seen by one of us, and his only complaint was that he had a bad odor to his breath. He had no cough or fever, and no constitutional signs. Physical examination of his chest revealed no abnormality. The radiograph, however, showed a definite cavity containing a fluid level in the left upper lobe. Over his protest, this patient was sent away for six weeks during which time he had no constitutional symptoms, and coughed and brought up sputum only on a few occasions. At the end of six weeks, a film of his chest showed a spontaneous healing of the abscess. This extraordinary experience has given rise to the suspicion that post-tonsillectomy lung abscesses may be present more often than we suspect. It would be interesting to make films of large series of patients two weeks after tonsillectomy to ascertain how frequently these unsuspected abscesses may occur.

C. Pneumococcus Pneumonia following Tonsillectomy. Pulmonary complications other than abscesses may follow tonsillectomy. A woman aged forty-two years (No. 229), developed acutely pulmonary signs twenty-four hours after tonsillectomy under local

anesthesia. This, however, happened to be an acute pneumonia (Pneumococcus I) (Fig. 12). The course was typical, the crisis occurred on the seventh day, and recovery was complete.

D. Activation of Pulmonary Tuberculosis following Tonsillectomy. Another atypical experience occurred in a girl aged twelve years (No. 175), who developed signs in the right upper lobe (Fig. 13) three weeks after tonsillectomy under general anesthesia. She had a Type I pneumococcus in her sputum. A radiograph showed a pneumonia in the right upper lobe and submiliary deposits throughout the whole lung, the latter suggesting tuberculosis. Films taken three weeks later showed no change, though the patient was not particularly ill. Later, tubercle bacilli were found in the sputum, and it became clear that the operation had activated a chronic tuberculosis (Fig. 14). An experience like this illustrates the necessity of a careful examination of the chest before operations on the nose and throat. Not only is this important from the standpoint of the determination of operative risk, but also for the interpretation of the postoperative clinical picture.

IV. Lung Abscess following Dentistry. Recently we have seen three instances of the development of lung abscess following extensive dental work. An example of this occurred in a man aged forty-five years (No. 273), who developed a lung abscess (Fig. 15) following a two-hour session in the dental chair under block anesthesia. His sputum contains numerous spirochetes, but he has not been helped by arsphenamin or bronchoscopic washings. We suspect that the air pressure used by dentists may possibly be a factor in the production of these abscesses, particularly when the patient is under anesthesia or when the gag reflex is insensitive, as occurs in so many patients. Certainly this idea is suggestive, and might warrant investigation by those competent to carry out such studies.

V. Foreign Bodies. In dealing with an atypical pulmonary condition, one should always bear in mind the possibility that an unsuspected foreign body may be present. Here the aid of the bronchoscopist is indispensable, from the diagnostic standpoint as well as from the therapeutic. The radiograph may not often reveal the foreign body.

A rather interesting variant of the picture occurred in a boy aged nineteen years, (No. 169), who entered the hospital for the relief of repeated hemoptyses. Radiographic (Fig. 16) and clinical examination showed a bilateral apical infiltration that resembled tuberculosis. Bronchoscopic examination was made and a walnut shell was removed from the left lower bronchus. The hemoptyses have not returned in the eighteen months that have elapsed. The boy has no constitutional manifestations of tuberculosis, and regards himself as perfectly well, though five months ago he was readmitted to the hospital with an acute bronchopneumonia of the right lower lobe, from which he also made a complete recovery.

VI. Influenzal Pneumonia. In times when influenzal infection is not prevalent, the classical influenzal bronchopneumonia[7] may escape detection, as was evidenced in a case of a man aged forty-two years (No. 223), who for three weeks had had cough and blood splitting with fever. A radiograph showed a dense shadow extending outward from the root of the right lung almost to the periphery and up to the apex. There were also a few indistinct shadows in the left upper lobe, and it was the opinion of the clinician and the radiologist that the Roentgen appearance was that of a carcinoma of the lung with metastases. The patient died and at autopsy a typical influenzal bronchopneumonia was found and no evidence of metastases. The unusual susceptibility of the patient was probably explained partially on the basis that he had a chronic nephritis and a terminal pericarditis.

VII. Pulmonary Manifestations of Acute Rheumatic Fever.[8,9] Pulmonary manifestations of acute rheumatic fever are seen less frequently in this country than in England. At times the pulmonary signs may precede the characteristic arthritis and the endocarditis. This occurred in a boy aged fifteen years (No. 239), who had a broncho pneumonia and was discharged from the hospital as relatively well. Three months later he was readmitted with slight fever and persistence of the pulmonary signs (Fig. 17). While under observation, he developed an acute arthritis, and the administration of salicylates resulted in the relief of both pulmonary and arthritic conditions.

VIII. Lobar Pneumonia. Odd variants are seen when one studies series of patients with lobar pneumonia. Pneumonias of brief duration are uncommon. A definite two-day pneumonia occurred in a woman aged forty-two years (No. 177), who came to the hospital with a clear-cut history of not more than one day of fever and cough. Signs of consolidation were present in the left axilla and left base. A crisis occurred before she was in the hospital twenty-four hours, and her convalescence was uneventful. Radiographs showed a definite pneumonia of the lower half of the right upper lobe (Fig. 18).

Pneumonia occurring in a syphilitic may at times give rise to some difficulties, for we have seen several instances in which failure of resolution occurred. A woman aged forty years (No. 29), went through a severe Type III pneumonia and recovered. She was known to have active syphilis, and the blood Wassermann reaction was 4 +. At the end of six weeks the lung signs still persisted and the suspicion arose that the process might be tuberculous. Under large doses of iodids her lungs finally cleared.

The more complicated variant of the same process occurred in a Porto Rican aged thirty years (No. 254), who entered with both primary syphilis and a right lower lobe pneumococcus pneumonia. He died almost immediately after admission to the hospital and was found to have, in addition to the syphilis and the fresh pneumococcus pneumonia, a tuberculous pneumonia of the left upper lobe.

The pulmonary condition may be luetic, as in the instance of a colored woman aged forty years (No. 123), who entered the hospital for the relief of substernal pain. Radiographs revealed diminished aëration of both bases, a mottling of both lower lobes and a retraction of the diaphragm. The whole picture suggested a fibrosis of the lung such as has been described in syphilis.[10] The blood Wassermann test was 4 +. She suffered very little and was discharged from the hospital. Three months later films showed no change in her pulmonary condition, though the patient was then working and is still at work. Very likely the pathologic condition here was a syphilitic fibrosis.

Despite extensive consolidation, patients with pneumonia may appear so well that the diagnosis is held in some doubt. Such an instance occurred in a man aged forty-four years with a three-day history of respiratory infection and signs of an involvement of the right lower lobe. The patient (No. 178), was so comfortable that his appearance suggested that this might be an effusion. Aspiration of the chest was negative, however; the temperature subsided, and the patient made an uneventful recovery. Another instance of the same kind occurred in a man aged twenty-eight years (No. 215), who had a three-lobe pneumonia and his blood culture revealed Type II pneumococcus, too many colonies to count. Despite this, the man was sitting up in bed without dyspnea or cyanosis, and it was with some difficulty that we were able to keep him in the hospital.

Nonpneumonic pulmonary complications may also occur in lobar pneumonia. A most unfortunate experience occurred in a man aged thirty-two years (No. 232), who entered the hospital during the crisis of a lobar pneumonia (Fig. 19). Three weeks later he was permitted to get up, and a radiogram showed what appeared to be a fresh consolidation at the site of the old consolidation (Fig. 20). That this interpretation was erroneous was proved two days later when he suddenly collapsed and died. Autopsy revealed a healed infarct of the lung at the site of the first consolidation, and a fresh thrombosis of the pulmonary artery.

IX. Pulmonary Tuberculosis. Tuberculosis frequently furnishes atypical lung signs and surprises for the clinician. Perhaps the two most striking examples that we have seen in recent years occurred in two women who entered the hospital simultaneously on the service of Dr. Baehr. The first was a girl, aged seventeen years (No. 242), who had no complaint other than vomiting. The house officer, Dr. Matzner, discovered chorioid tubercles, and despite the absence of pulmonary signs, ordered a radiograph, which showed a miliary tuberculosis of an advanced type (Fig. 21). She was observed for some weeks during which time she developed no pulmonary symptoms, but later a tuberculous meningitis proved fatal. At the same time there was present in the ward a woman

aged thirty-three years (No. 243), who complained of weakness and cough for two weeks. Her chest was normal to routine examination, but radiograph showed a subacute miliary tuberculosis (Fig. 22) with extensive involvement. During five weeks' observation, she developed no clinical lung signs, had no fever and gained 5 pounds. She was discharged and sent to the Montefiore Hospital, where she stayed until June, 1927. Her temperature curve there was of the subfebrile type. She gained another 7 pounds, and is apparently doing perfectly well, though the radiographic films show a diffuse stippling of a nodular type over both lung fields.

X. Neoplasms of the Lung. Neoplasms of the lung are now being met much more frequently than ever before. Whether the disease is on the increase or whether, with the aid of the radiograph and bronchoscopy, we are making the diagnosis with more accuracy, can only be decided by statisticians. The possibility of neoplasm must always, however, be borne in mind, and the findings and course may be very atypical. As an example of the difficulty with physical signs, we might cite the instance of a man aged fifty years (No. 271), who entered the hospital for the relief of cough, fever and dyspnea of three weeks' duration. He was sent in with the diagnosis of pneumonia, but his lung signs were very atypical, and suggested an atelectasis of the left upper lobe. It was suspected that he had a ball-valve tumor of the bronchus which accounted for the atelectasis, the peculiar dyspnea and the cough. This was confirmed by bronchoscopy and later by autopsy.

Metastatic carcinoma may develop in the lung, long after the primary lesion: the following instance exemplifies such an occurrence, seventeen years after the removal of a bladder carcinoma. This patient (No. 251), (Fig. 23), was a man aged fifty-one years, who had a complete situs inversus, and who entered the hospital for pulmonary signs. Radiographic films suggested the appearance of carcinomatous infiltration, but the old history was so far separated from the present symptoms that it seemed unlikely that there was any relationship. At autopsy, however, a single malignant area was still present in the bladder region, and it corresponded histologically to the lung infiltration.

Many individuals with lung neoplasms suffer very little and go along comfortably for a long period of time. Such was the experience of a man aged forty-three years (No. 50), who was first seen in May, 1925, for the relief of an arthritis. Routine examination revealed a large shadow of the right upper lobe which was definitely neoplastic in appearance. He has received radiographic therapy since. The pulmonary condition is unchanged; he has gained 23 pounds, and is in perfect physical condition. The diagnosis, may, of course, be open to doubt, but certainly anyone seeing him for the first time would definitely give him a very ominous prognosis.

XI. Atelectasis of the Lung.. Atelectasis of the lung may occur in the massive collapse already described. In this instance, the mechanism is probably neurogenic. Pressure atelectasis may also occur, as in the instance of the ball-valve tumor of the bronchus already described. At times it is difficult to understand the mechanism of the atelectasis, as in the instance of a woman aged fifty-two years (No. 70), who had had asthmatic attacks for five years. Radiographs showed a pneumonic infiltration of the left lower lobe. On bronchoscopy it was found that this lobe was atelectatic. Under bronchial washings and dilatation, the patient made an uneventful recovery. The radiograph was normal in six months, and the patient was completely relieved of her asthmatic attacks.

Another example of atelectasis occurred in a child aged eighteen months (Fig. 25). She was seen by one of us in an attack of cyanosis and dyspnea that was so severe that the child was not expected to live. Clinical examination revealed a collapse of the right upper lobe, and this was confirmed by radiograph. This film showed in addition to the collapsed lobe, an enlargement of the thymus, and on the theory that the collapse might possibly be due to thymic pressure, radiographic treatment was instituted by Dr. Samuel Stern. The child seemed to do very well for a time, and then the symptoms returned, and she was admitted to the Mount Sinai Hospital. At this time the child was practically moribund. A bronchoscopic examination was made and the upper lobe was found collapsed. Though no therapy was instituted, the child improved remarkedly following this examination, and has remained well now for three years. A radiogram taken recently shows the upper lobe to be aërated, but in the region of the eparterial bronchus is a calcified shadow, which is probably a tuberculous node. In retrospect, it seems more likely that the pressure was caused by the gland rather than the enlarged thymus.

Summary. We have reported a number of unusual experiences in the study of intrathoracic diseases. Some of these are queer variants of common abnormalities, and others represent unusual pathological pictures, but all illustrate the necessity of coöperation between clinician, radiologist and bronchoscopist. At this time we need not emphasize the necessity of radiographic examinations in obscure pulmonary conditions. Bronchoscopy, however, is not sufficiently employed, and we regard it as a necessary procedure in obscure pulmonary conditions. Neither the radiologist nor the bronchoscopist, however, should attempt the interpretation of findings without the assistance of the clinician, for it is to him that they must look for the background and for the record of the clinical findings, neither of which can be seen on a film nor observed through a bronchoscope.

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THOUGHTS ON THE MORBID PROCESSES ACTIVE IN PERNICIOUS ANEMIA.*

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Claude Bernard's well known advice to "put off your imagination as you take off your overcoat when you enter the laboratory," contains the equally important clause: "but put it on again, as you do your overcoat, when you leave the laboratory." Perhaps it may even be occasionally worn in the somewhat chilly medical society meeting room. Hence a few speculative remarks on the mechanism at fault in pernicious anemia may not be out of place at a time when much thought is being given to the problem and when Minot and Murphy's study of the effect of liver (and liver extract) diet suggests further insight into the disease.

In the present classifications of the anemias, pernicious anemia will be found, and still rightly I think, among the hemolytic anemias; but exception might be taken when it is classed, as is often the case, as "primarily due to increased blood destruction." The disease is unquestionably more than a matter of increased cell destruction—for instance, the increase in hyperplastic hemopoietic tissue is much greater than the increase in blood destruction—and it seems perhaps more consistent with recently established facts to agree with Minot[1] that a more fundamental defect of the hemolyto-poietic system may be the inability to form efficient erythrocytes, which consequently and therefore only secondarily are destroyed in increased numbers. In fact, the very existence of a state of increased blood cell destruction has been questioned, wrongly I think, as to me it is hard to picture (as some have done) that the increased urobilin content of urine and feces, the high icterus index, the well-known phagocytosis and

* Read before the Philadelphia Pathological Society, February 9, 1928.

deposition of pigment in the viscera are all signs, not of increased blood-cell destruction, but of elimination of hypothetical materials designed for hemoglobin formation, but unavailable in the hemoglobin saturated state of the few functioning erythrocytes in this disease.

Granted for the moment, however, that the increased blood-cell destruction may represent the elimination of unfit cells (just as in familial hemolytic jaundice, it is probably due to the elimination of congenitally fragile cells), we should next inquire how and why these cells are unfit, and to such a question no complete answer can yet be made. However, Minot's and Peabody's confirmed observations of the behavior of the reticulocyte count, and of bioptic (that is, obtained at biopsy) bone marrows in cases rapidly improving under the liver diet, show such a marked and transient rise of the reticulocytes and a progressive change of the bone marrow from the crowded megaloblastic to the normal appearance, that it is difficult to avoid Minot's conclusion that some substance in the liver (equally present in the liver extract) interrupts the pernicious process and permits the laboring bone marrow, after a short excess of over (but tending toward more normal) production, to settle down to normal and more efficient activity. In passing, the improvement following kidney feeding* must neither be forgotten nor allowed to usurp too much attention—insulin is rightly considered a specific product of the islands of Langerhans and yet blood sugar can be lowered by the products of other body tissues or even vegetable substances.

Believing that anemia is but one feature of this complex disease, we must assume that the unknown beneficent substance in the administered liver also combats the noxa that causes the other cardinal features of the disease (glossitis, nervous system changes, etc.) as they too seem to be ameliorated, or checked, in the Minot treatment. The question as to whether the active liver substance is a vitamin, hormone, detoxicant or still some other kind of agent, or whether it merely replaces something absent or deficient in the pernicious anemia liver is one that we may hope will be solved by the work that Minot and Murphy's papers have stimulated. Whipple[9] has for several years advocated the point of view that pernicious anemia is a deficiency disease—and more specifically, due to a deficiency in materials that build the stroma of the erythrocyte. The analogy of several pernicious anemia symptoms to those of other deficiency diseases such as pellagra, beri-beri and sprue (if perchance sprue belongs in this class) must also be borne in mind.

The above considerations might make one lean toward the detoxifying theory, as one naturally thinks of other detoxifying functions ascribed to the liver. It must be confessed, however, that the

* Since this paper was sent to press a short article by McCann (Proc. Soc. Exp. Biol. and Med., 1928, **15**, 255) shows that at least almost as good result can be got, at least temporarily, by feeding kidney.

efficacy of the simpler chemical form of the liver remedy removes it such a distance from a functioning liver that detoxification, other than by the improbable simple chemical union, becomes difficult to visualize.

In any case, we have climbed one more rung of the ladder. If one might consider the excessive blood-cell destruction as the fourth big step in the morbid process, then the third would be the dyspoiesis of the bone marrow, which would be of the same generation as the glossitis, diarrhea, nervous system degenerations, etc.

A conception of the second step must still be necessarily a hazy one. That the liver is intimately concerned is evidenced by the prompt and striking improvement that follows ingestion of liver; but we have already touched upon the varied possibilities of its mode of action. That the spleen is also intimately concerned is indicated by the prompt improvement (even though temporary) that usually follows splenectomy. The frequent so-called blood crises after splenectomy in pernicious anemia (temporary flooding of the circulation with normoblasts) and the coincident rise in reticulocytes suggests a similarity to the action of the liver extract, which though it does not permit one to say that the diseased spleen was preventing the liver from exerting its normal effect upon the bone marrow, or still less that splenectomy had the same effect as feeding liver, nevertheless points in no uncertain manner to the participation of the spleen in the pernicious anemia process and to the hepato-lienal relationship, so ably shown by Eppinger[2] some years ago. Our experimental observations of some years ago, since amply confirmed, that removal of a normal dog's spleen, or diversion of the splenic blood from the liver, is followed by a characteristic transient anemia of moderate degree, indicated to us that the normal spleen secreted into the blood something which after passage through the liver exerted a stimulating effect on the erythropoietic function of the bone marrow. With this in mind, it becomes difficult at first (but not impossible) to picture how removal of a spleen, which to be sure is diseased, is followed, as it so often is, by the opposite effect on the blood picture (that is, a rise in the blood count); but this only makes one realize that the spleen is a complex organ of several functions and in pernicious anemia not only may its hemolytic function be overshadowing (hypersplenism), but it may well have some other influence in preventing the liver from exerting a "maturating" effect on the erythroblasts, a defect supplied by feeding normal liver. It would indeed be interesting to try on pernicious anemia patients the effect of liver extract prepared from pernicious anemia liver, both from splenectomized and nonsplenectomized patients.

Consideration of the possible primary cause of the disease must necessarily be a very incomplete one, both on account of the great number of hypotheses that have been advanced since physicians first began to balk at the term "idiopathic" and also because there

is, alas, but little profitable to add. To those who would look at the diagnosis "pernicious anemia" as covering a group of diseases, we should say that due to our imperfections perhaps it still is today, even though we can and should split off various secondary pernicious anemias, such as Bothriocephalus anemia, the so-called pernicious anemia of pregnancy and other chronic anemias with similar blood pictures, just as various diseases have from time to time been split off from the original concept of splenic anemia. Nevertheless granted that subgroups still await recognition, there may always remain a fairly common condition, due to a single cause or chain of causes, for which the term "primary pernicious anemia" might be reserved and it is with this that we are chiefly concerned.

It will be seen that even for a speculative paper this has its fair share of "mights," but as one advances to consider the primary link in the chain, there are still more "ifs" and "mays" and no striking new theory has been recently added to those that for a number of years have been advocated without being proved. We may assume that achlorhydria is probably a constant but preceding and otherwise unrelated accompaniment of the disease (Hurst[3]), and that other predisposing factors must of course be considered. I need no more than mention the chief types of causative agents that have been advanced: some unknown intestinal ptomain or infection perhaps entering the intestines through the unguarded stomach (Hunter[4]), a certain (or rather uncertain) chronic cholecystitis, an intestinal toxemia (K. Faber[5]) (especially of Bacillus welchii (Moench, Kahn and Torrey[6]), a hypersplenism (according to some the result of intestinal infection or toxemia), a disturbance of lipoid metabolism with an accumulation of hemolytic unsaturated fatty acid (Eppinger), etc. The relation of infection to pernicious anemia has recently been well covered by Evans.[8] That pernicious anemia serum contains a substance injurious at least to plants has recently been demonstrated by Macht.[7] All these causative agents have their advocates as the cause of pernicious anemia, but perhaps a still larger number of opponents. I think it is safe to say that none has even approached proof; just as one can safely but unfortunately say that the real disease has never been produced experimentally. As nonspecific *contributing* causes they are more intriguing, especially when one thinks of possible coöperation with other contributors, such as the intestinal growth permitted by the achylia, its tendency to aid sporulation of the Welch bacillus, the effect of stasis on intestinal putrefaction,[4] the colonization of Monilia that diets deficient in vitamin permits and so on.

From the evidence at hand and *a priori* reasoning, one leans toward an intestinal noxa somehow associated with achlorhydria, and absorbed by the portal system. This hypothetical noxa may in turn in its passage through the spleen stimulate it to excessive hemolysis, as well as damage its normal relation to the hemopoietic

function of the bone marrow. Arriving in the liver, it may upset that organ's hypothetical relation to hemopoiesis (perhaps hindering it in furnishing a necessary ingredient) with the result that inefficient erythrocytes are prematurely ejected into the blood stream or their maturation delayed and disturbed, so that in spite of the marrow hyperplasia an insufficient number of inefficient erythrocytes are turned out, to be destroyed in excessive numbers, as is well recognized in the pathologic anatomy and physiology of the disease.

If anyone objects to the number of "ifs" and "mays" in such a hypothesis, he will doubtless have the satisfaction of knowing that today he has many companions, but he might perhaps ponder on Reed's reaction to Finlay's equally hypothetical views on the yellow fever mosquito.

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THE DIAGNOSIS OF SPORADIC INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER).

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INFECTIOUS mononucleosis, like many other diseases of unknown etiology, has been designated by the names of its two outstanding features. Filatow (1885) first regarded it as an idiopathic cervical adenitis. It seems to be identical with the epidemic glandular fever,[1] first described by Pfeiffer,[2] who thought it always occurred in children. Downey and McKinley[3] have called the disease acute lymphadenosis, a name hardly more descriptive than infectious mononucleosis. They do not believe it identical with glandular fever because of the highly epidemic nature of the latter and the absence of marked tonsillitis or pharyngitis.

The diagnosis of the condition may be inferred by the symptoms, including acute lymphadenopathy, but can be confirmed only by

blood studies. The disease is rarely fatal, but troublesome complications may arise. The clinical similarity that it bears to the common upper respiratory infections and influenza undoubtedly causes it more often than not to be confused with them. Vincent's angina[4] may also obscure the underlying disease. Unless adenopathy be prominent or the course be relatively prolonged, the practitioner may not suspect the true nature of the illness. Where routine blood differential counts are practised, a much higher percentage of correct diagnosis can be made. The ability to make a diagnosis is occasionally of great importance from the prognostic viewpoint, as the disease has been confused with tuberculosis, typhoid fever, leukemia and Hodgkin's disease.

The publication of Sprunt and Evans in 1920,[5] and later that of Longcope,[6] served to establish the disease as a clinical entity in this country. Similar blood pictures had been previously described by Türk,[7] Lüdka,[8] Marchand,[9] Cabot[10] and Sanders,[11] in patients with infections usually having their origin outside the upper respiratory tract.

Tidy and Daniel[1] studied an epidemic from the viewpoint of the identity of the disease with glandular fever. They believe that the identity is certain, but prefer to continue to call it glandular fever. The disease, as they have described it, is characterized as an acute, infectious and contagious disease, usually occurring in children. It is accompanied by rapid enlargement of the spleen and of axillary, inguinal and other lymph nodes. Some tenderness occurs in the cervical glands, but they are not acutely painful; abdominal pain is occasionally severe. The fauces are usually reddened, and the tonsils may be enlarged, but exudate is unusual, the changes being remarkably slight compared with the glandular enlargement. There is no anemia in the acute stages. There may be a short period of malaise, the glands appearing about the third day and reaching a maximum in one to three days. Fever usually under 103° appears with the swelling of the glands. This may occasionally reach 105° for a day or two but it rarely exceeds 100° for more than a week. The enlargement of glands usually subsides in five to fifteen days, but may recur, or, if unilateral, may occur on the opposite side. Suppuration is very rare. The glands remain palpable for several weeks or for months. There is usually a prolonged period of slight depression of health and anemia which needs attention. In about 6 per cent, hemorrhagic nephritis occurs.

The most exhaustive cytologic study of the abnormal cells in the disease is that of Downey and McKinley[3] who made a tentative classification of the cells into three types which are useful in the study of the condition. They belong to the lymphocytic series and none of the cells showed the immaturity found in lymphatic leukemia. No clinical signs were noted by which the type of predominant cell could be predicted before cytologic study. Their Type I

cells are most common. They are not excessively large and vary much in size and shape. They are highly differentiated lymphocytes (Pappenheim) rather than immature "lymphoblasts." The nuclei, often eccentric, are lobulated and irregular. Some are kidney shaped. The chromatin forms a course network of strands and masses, not sharply differentiated from the parachromatin, producing the characteristic cloudy appearance of the lymphocyte. Some of the larger cells show a slight tendency toward a more diffuse arrangement of chromatin, but not sufficiently to justify classification as immature. The degree of basophilia of the cytoplasm is greater than is usual in the large lymphocyte or large mononuclear. It varies somewhat in intensity. The spongioplasm stains dark blue or slate-blue, finely granular (see ground-glass appearance of Sprunt and Evans) or flasky, in a pale-yellow background of hyaloplasm. The relative amounts of spongioplasm at the periphery and at the indentation of the nuclei cause the cells to be more heavily stained at the former and more lightly at the latter localities. Many of the cells have azurophilic granules in the cytoplasm. Vacuolization of the cytoplasm is not infrequent.

Type II cells present less variation. They are large and resemble plasma cells, but they have a more washed appearance and the chromatin condensation is not so marked. The cytoplasm is more homogeneous and does not have the vacuolated, spongy or stippled appearance as in Type I.

Their Type III cells are the largest and resemble leukemia cells more than the other two types. Some of the nuclei are diffusely vacuolated and contain one or more nucleoli, resembling leukemia cells. They are fairly regular and are rarely lobulated. Numerous intermediary cells between the extremes are present. The cytoplasm stains less heavily than Type I and more heavily than Type II, and is more vacuolated than either of the other types. About 1 per cent of the cells contained an azurophilic rod in a large vacuole at the identation of the nucleus.

The literature on infectious mononucleosis is now fairly extensive. It has passed through a period of development along two converging lines. The first line consists of reports on the epidemic occurrence, principally in children. The second has been concerned with sporadic cases usually confused with leukemia. The first such case was reported by Hall[12] in England. Osler, in discussing Hall's case, mentioned a similar case which recovered after arsphenamin treatment. Barker[13] in this country included in his series of acute leukemia cases one which he regarded as an infection rather than a true leukemia. More recently, Krumbhaar[14] described a case in his article on Leukemoid Blood Pictures. Not infrequently Vincent's angina confuses the picture. Deussing's[15] report of 3 such cases and White's[16] case are other instances of these.

After the two lines of observation become confluent, sporadic and

epidemic cases have been better studied. Sweeting's[17] observations on an epidemic in New York stimulated an intensive study of several epidemics there. A personal communication from Dr. C. R. Hervey, district state health officer, stated that Sweeting's cases were in the third epidemic coming to his attention. This epidemic was marked by a contagiousness as great as that of measles. Sweeting noticed a transient glycosuria in a few cases and attributed it to involvement of the pancreas. Dr. Harvey also mentioned cases having sufficient mediastinal enlargement to be demonstrable by Roentgen ray plates. Gilbert and Coleman[18] studied 100 of these epidemic cases. Streptococcus hemolyticus was isolated from the pus of an axillary gland and from four of seven throat cultures. Streptococci producing methemoglobin were found in six of the seven throat cultures. Carlson, Brooks and Marshall[19] described an epidemic of glandular fever of over 838 cases, and reported data on 79 patients. Throat cultures showed in 46, streptococcus; in 28, Staphylococcus aureus hemolyticus; in 3, a diplococcus; and in 2, a fusiform bacillus. During the past five or six years, other reports have come from Brazil,[20] Australia,[21, 22] Scotland,[23] and several widely separated states in this country,[24, 25, 26, 27, 28, 29, 30] but the report of Baldridge, Rohner and Hausmann[31] is perhaps the most comprehensive. Four-fifths of their patients were University of Iowa students, nurses or physicians. The youngest patient was six and a half years old, the oldest a man of forty years. They suspect that the streptococcus is probably the etiologic agent. Examination of the biopsy specimens in the glands of 6 patients did not reveal clues that had not been elsewhere reported.

Duncan[32] in South Africa described a number of patients which he believes may be related in some way to tuberculosis. The blood pictures of this "Karoo syndrome" was not studied. The description is strikingly like the sporadic cases of infectious mononucleosis. This similarity has been called to his attention by a number of people. In a personal communication, he points out that the Karoo syndrome differs from infectious mononucleosis by its sporadic occurrence, its chronicity, and recurrences over a period of years, the small lymph nodes and lack of splenic enlargement. However striking this similarity may be, blood studies should be made in order to exclude it from serious consideration.

Fox[33] and Cottrell[34] have published detailed clinical studies of infectious mononucleosis as well as descriptions and photomicrographs of biopsy material.

Description of Patients. The following patients have been encountered over a period of four years and their histories are reported below in the order of their occurrence. It is worthy of note that all of these patients had the cells which Downey designates as Class I.

Case Reports. CASE I.—*A Case Diagnosed as Influenza, in which the Blood Count Revealed Infectious Mononucleosis.* H. B. M., white, male,

TABLE I.—THE BLOOD DATA OF H. B. M.

Date.	R. B. C.	Hgb. (%).	W. B. C.	Percentage.			Mononuclears.			Transitionals.	Unclassified.	Cells counted.	Remarks.
				Neutrophils.	Eosinophils.	Basophils.	Large.	Small.	Abnormal.				
4–15–23	5,400,000	85	15,000	22.80	0.77	..	...	7.0	66.32	3.11	..	386	
4–16–23	.....	..	13,000	25.20	1.55	0.77	?	9.69	61.24	1.55	..	258	
4–17–23	.....	..	12,000	29.29	1.40	..	3.25	7.44	53.00	6.04	..	215	
4–18–23	5,200,000	..	12,000	19.00	1.64	0.32	6.20	9.50	58.36	2.72	1.90	305	
4–20–23	.....	..	10,000	20.33	1.08	..	8.67	11.65	54.74	3.52	..	369	0.6 gm. neoarsphenamin.
4–23–23	.....	..	10,000	27.51	0.30	..	12.03	22.60	35.06	1.14	1.14	349	
4–25–23	.....	75	6,000	35.21	0.62	0.31	9.00	20.00	33.75	1.25	..	314	Better; attending classes.
4–27–23	.....	..	6,000	32.40	1.03	..	5.15	29.27	29.27	2.85	..	320	
4–30–23	.....	..	6,400	38.55	1.20	0.72	7.47	40.72	10.87	0.25	..	386	
5– 2–23	.....	..	6,000	35.26	2.54	1.27	5.00	46.46	9.00	0.64	..	415	
5– 5–23	.....	..	5,000	39.00	1.52	0.70	4.40	52.00	5.50	1.30	..	312	
5– 8–23	.....	..	5,000	38.80	2.30	0.50	8.05	44.54	5.74	2.80	..	456	
5–12–23	.....	..	5,000	27.12	1.60	0.54	9.50	55.00	5.40	0.80	..	348	
5–16–23	5,600,000	80	7,000	52.00	2.00	..	11.00	32.00	2.00	2.00	..	369	Regular work; glands still palpable
5–19–23	.....	..	5,000	40.30	2.80	..	9.70	45.80	...	1.40	..	250	No apparent infection to account for neutrophil increase.
5–23–23	.....	..	5,000	37.50	3.00	1.50	14.29	39.29	...	5.39	..	360	
5–28–23	.....	..	6,000	40.00	2.94	..	7.35	48.50	...	1.47	..	280	
6– 2–23	5,000,000	80	6,000	42.40	1.60	..	6.70	49.00	...	...	..	340	
7–16–23	5,850,000	90	8,750	44.60	0.60	..	?41.00	6.50	?41.00	7.10	..	295	Acute pharyngitis and tonsillitis; Health good; no known infection.
12– 1–25	.....	..	....	56.15	3.66	0.36	12.68	18.11	...	8.70	0.72	...	

aged twenty-seven years, medical student, was admitted to the hospital complaining of sore throat, weakness for two weeks, general irritability and insomnia. His illness began eighteen days before admission to the hospital with malaise, tonsillitis, pharyngitis, coryza and weakness. He was confined to bed five days. After resuming his classes for a day or two he was too weak to continue. The throat had cleared up, but six days before admission it again became sore. The weakness persisted and insomnia began. Hot baths, strychnin and sodium benzoate were administered without beneficial effect. At one time he had a temperature of 99.5°, and there was general muscle soreness and frontal headache.

Physical examination revealed him well nourished and developed. Prostration was moderate. A positive Ewing sign was present bilaterally. The inferior nasal turbinates were injected and covered with mucopurulent exudate. The conjunctivæ were somewhat injected. The sinuses were all acutely inflamed; the faucial tonsils were slightly enlarged and of a bluish-red color; the lingual tonsils were very red and swollen. The pharynx, larynx and epiglottis were red and edematous. There was firm discrete adenopathy of submental and anterior and posterior triangles of the neck extending down to clavicles. Deglutition was difficult. The lungs were normal. The blood pressure was 125 systolic and 70 diastolic. The heart was normal. Tenderness was definite at McBurney's point. The liver and spleen were not palpable at first, but two days later the spleen was easily felt. Discrete inguinal, axillary and epitrochlear lymph nodes were palpated. All tendon reflexes were sluggish. The prostate was slightly tender and its secretion showed many pus cells.

The temperature varied from 37.6° to 38.2°, falling in a day or two down to 36.6°. Smaller variations occurred daily until discharged. The patient gradually improved and was given 0.6 gm. of neoarsphenamin the day before discharge. The throat culture showed hemolytic streptococcus and Staphylococcus aureus. Dark-field examination of tonsils showed numerous short and actively motile spirochetes. A biopsy specimen of a lymph node from the neck revealed a chronic inflammatory reaction. Diphtheroid organisms were obtained from a culture of the macerated gland. The blood Wassermann was negative. The prostatic secretion contained no organisms. The gonococcus fixation test was 2+. The blood culture was negative. Phenolsulphonephthalein renal function test was 70 per cent in two hours. The urine contained a slight trace of albumin on one occasion and a few pus cells on several occasions.

The patient was well for six weeks when he had tonsillitis, pharyngitis and severe headache. He was readmitted to the hospital July 17, 1923, at which time there was some suspicion of meningitis. The lymph nodes had diminished much in size, but the number of lymphocytic cells was increased. He has remained in excellent health during the last four years.

CASE II.—*A Case Suspected of Leukemia.* E. C. D., white, female, aged forty-three years, housewife, was admitted February 13, 1922, complaining of headache, weakness, nasal trouble and constipation. Frequent sore throat occurred during childhood. She had typhoid at twenty-seven years of age with prolonged convalescence. The typhoid aggravated a pain in the right upper quadrant for a while. Chronic sinusitis and susceptibility to colds were troublesome. Malaria occurred four years before. For two years the teeth were known to have apical abscesses. One year previously she had arthritis. The appetite had always been capricious.

Her present illness began five or six weeks before admission. She was in bed two days with fever and a cough productive of considerable mucus. The nasal secretions were blood-streaked. Weakness, poor appetite, dizziness, headache, photophobia and some insomnia had persisted. Following a vaccination performed two weeks previously, nausea, flatulence

and constipation had been present. She was poorly nourished. The vaccination sore was receding. A slight conjunctivitis and refractive error were present. The thyroid was slightly enlarged. No cervical lymphadenitis was noticed. Chronic hyperplastic ethmoiditis, tonsillitis, otitis media and apical granulomata of teeth were present. The blood pressure was 95 systolic and 50 diastolic. The liver was not enlarged but the spleen was palpable on deep inspiration.

TABLE II.—BLOOD FINDINGS OF E. C. D.

Date.	R. B. C.	W. B. C.	Hgb. (%).	Lymphocytes.	Mononuclears.	Neutrophils.	Eosinophils.	Basophils.
2–13–22	4,160,000	9,350	90	36.0	24.0	31.0	7.0	2
2–14–22	....	11,000						
2–15–22	4,660,000	10,100	90	28.0	25.0	35.0	10.0	2
2–18–22	4,680,000	9,550	90	36.0	21.0	33.0	10.0	
2–20–22	....	8,500	90	22.5	15.5	60.5	0.5	1
2–23–22	....	7,200	..	17.0	20.0	61.0	2.0	
2–26–22	....	10,000						
2–28–22	....	9,500						
3– 2–22	....	9,300	90					
3– 9–22	3,920,000	....	75					

The patient was put on a high-caloric diet, all suspicious teeth were extracted and the sinuses were drained surgically. The blood picture was noticed to be abnormal and studied from the standpoint of leukemia. The type of lymphocytic increase indicated infectious mononucleosis. The temperature, pulse and respiration remained normal. The blood Wassermann was negative. The blood nonprotein nitrogen was 41.1 mg. The basal metabolism was normal. The phenolsulphonephthalein renal function test was 70 per cent in two hours. The urine showed a constant trace of albumin. The stools were normal. The abnormal nongranular large lymphocytes gave a negative oxidase reaction. The clotting time was about twice normal. There was considerable oozing of blood after the nasal operation. A biopsy specimen of a lymph node was studied, but a record of it was not found in the hospital history.

CASE III.—*A Case of Pleurisy with Unrecognized Infectious Mononucleosis.* H. B. W., white, male, aged thirty years, iron molder, was admitted March 5, 1923, complaining of severe pain in right side, cough and chilly sensation. A nasal obstruction was present and he had frequent colds due to fumes. On August 30, 1922, his foot was burned by molten metal, causing infection with lymphadenitis and fever. He was discharged from the hospital with a white count of 13,000; the blood cytology was not studied. The present illness began three days before admission with chilly sensations, fever and sweating. The pain in right lower side of chest gradually increased and he had paroxysms of unproductive cough which confined him to bed; after two days he tried to resume work but was too weak. The appetite was poor, and headache and photophobia were present on the fourth day of the disease. He was well-nourished. There was moderate prostration, and he had tenderness over both maxillary and frontal sinuses. Pus was washed out of the maxillary sinuses, the middle turbinates were hyperplastic and

pus was coming from right middle meatus. The tonsils were small and infected, the adenoids enlarged, and the teeth and gums neglected. The lymph nodes of upper anterior cervical triangles and the nodes along the posterior border of sternocleidomastoid muscles were enlarged but none were especially tender. A pleurisy was confirmed by Roentgen ray. There was a low-pitched murmur at the base of the heart and a sinus type of arrhythmia. The blood pressure was 103 systolic and 77 diastolic. The appendix region was definitely tender. Spleen was not palpable. The inguinal lymph nodes were moderately enlarged. At first the blood was considered negative, but on going over the blood smears a month after his discharge, the abnormal cells were discovered. A tuberculosis complement-fixation test was negative. The phenolsulphonephthalein renal function test was 56 per cent in two hours. Type IV pneumococci were found in the sputum. Dark-field examination of the sputum showed large coarsely spiralled spirochetes on three occasions. The stools and urine were negative. The temperature was 37.5° on admission but fell to normal the following day. Examination five weeks later and in October, 1924, showed generalized lymphadenopathy and abnormal cells. A pleural stripping sound on the right was still present five weeks after discharge. The appetite was variable and he had lost a few pounds in weight.

TABLE III.—BLOOD FINDINGS OF H. B. W.

Date.	R. B. C.	Hgb. (%).	W. B. C.	Cells.	Lymphocytes.	Large mononuclears.	Abnormal mononuclears.		Transitionals.	Eosinophils.	Neutrophils.	Basophils.	Remarks.
							Small.	Large.					
3- 6-23	5,230,000	80	8,150	200	2.5	1.5	42.5	9.0	6	0.5	37.5	0.5	Lymph nodes all small and hard.
4-23-23	4,150,000	90	8,500	166	7.2	0.6	30.1	1.8	3	1.2	56.0	0.0	
10-22-24	.....	..	..	362	?	0.3	42.9	0.8	1	1.6	52.1	1.0	

CASE IV.—*A Case Obscured by Insidious Onset.* T. L. R., white, male, aged twenty years, clerk, was admitted August 7, 1923, complaining of weakness, loss of ambition, pain in left hypochondrium. About July 1, 1923, the patient had a cold with a slight unproductive cough, dizziness, weakness and staggering gait. His physician told him that he had a "change in the blood and back pressure on the heart" and he was prohibited to work. There was no improvement except a gain of 3 pounds in weight.

He was somewhat undernourished. There was no sinus or mastoid tenderness. The tonsils were slightly enlarged and infected, and the adenoids were considerably enlarged. The left pupil was slightly larger than the right and a slight lateral nystagmus was present. The lymph nodes were palpable on the left side of the neck. The thyroid was barely palpable and smooth. The liver and spleen were not palpated. The inguinal glands were enlarged, the right more than the left. A small soft mass was present in the lower pole of left epididymis.

The blood Wassermann was negative. Blood nonprotein nitrogen was 26 mg. Albumin was present in variable amounts in the urine. Staphylococci and diphtheroid bacilli were found in a catheterized specimen of urine. The phenolsulphonephthalein renal function test was 63 per cent in two hours. The concentration diuresis was normal. Roentgen rays of the teeth showed apical abscesses. Vestibular tests indicated a toxic labyrinthitis.

TABLE IV.—BLOOD FINDINGS OF T. L. R.

Date (1923).	R. B. C.	Hgb. (%).	W. B. C.	Differential percentages.						
				Small lymphocytes.	Large lymphocytes.	Transitionals.	Neutrophils.	Eosinophils.	Large mononuclears.	Unclassified.
8– 8 . .	4,790,000	80	8,600	45.0	18.0	13.0	24			
8–14 . .	....	..	...	53.5	20.5	1.5	24	0.5		
8–15 . .	....	..	7,200	37.0	14.0	5.0	35	..	6	2

CASE V.—*A Case Confused with Typhoid and Malaria.* E. W., white, male, aged twenty-six years, chemical engineer, was admitted August 22, 1923, complaining of afternoon fever. The patient had otitis media bilaterally until tonsillectomy at eleven and seventeen years. Three weeks before admission, he felt a general malaise with frontal headache, painful ocular movement, chilly sensations, pain and stiffness in the back of the neck and in the back. His sleep was interrupted by profuse night sweats. He had a daily afternoon fever up to 102°. Malaise weakness and lassitude became worse during the first week. His first physician advised him that he had mild typhoid fever. A second doctor examined his blood and stated that malarial parasites were present. Quinine therapy did not cause any noticeable improvement. The afternoon fever, weakness and lassitude continued and the patient came into Barnes Hospital for diagnosis. He was well nourished and developed. An occasional dry cough was present. The nose and throat were normal. The tonsils were absent. The cervical lymph nodes in the anterior triangles and supraclavicular fossæ, both axillæ and inguinal regions were enlarged and fibrous to the touch. The liver and spleen were not enlarged to palpation or percussion.

The appetite was fairly good. Afternoon temperature rose regularly from 37.2° to 38.3°. The patient felt very little if at all improved and lost almost 3 pounds. Neoarsphenamin 0.3 gm., was given without any noticeable effect.

TABLE V.—BLOOD FINDINGS OF E. W.

Date (1923).	R. B. C.	Hgb. (%).	W. B. C.	Differential percentages.					
				Lymphocytes.	Large mononuclears.	Transitionals.	Neutrophils.	Eosinophils.	Basophils.
8–23 . . .	4,880,000	85	10,750	58.8	9.2	8.0	23.2	0.4	0.4
8–25 . . .	....	..	8,150	49.0	2.6	8.3	38.3	0.3	1.3
8–26 . . .	....	..	....	65.6	0	0.4	32.8	1.0	...
8–30 . . .	....	..	....	68.0	0	3.7	25.3	1.3	1.9

TABLE VI.—BLOOD FINDINGS OF G. L. S.

Date, 1925.	R. B. C.	Hgb. (%).	W. B. C.	Lymphocytes.				Large Mononuclears.	Transitionals.	Polymorphonuclears.			No. of cells.	Remarks.
				Abnormal.		Normal.								
				Small.	Large.	Small.	Large.			Neutrophils.	Eosinophils.	Basophils.		
5–22	4,000,000	80	20,350	16.1	64.6	0.3	0.6	..	0.3	17.1	..	0.6	304	Spleen enlarged to percussion.
5–23	.....	..	....	51.6	31.0	0.3	..	..	0.3	18.5	..	0.3	345	
5–24	.....	..	....	58.9	24.6	1.2	..	..	0.6	14.8	..	..	317	
5–25	.....	..	21,800	76.8	9.6	..	..	..	0.3	12.8	0.3	..	304	Lymph nodes smaller.
5–29	.....	..	8,600	63.0	20.3	0.6	1.0	..	0.3	14.5	..	..	295	
6– 8	.....	..	6,300	32.4	16.0	9.5	4.6	1.3	0.6	34.1	0.3	1.0	305	Glands smaller.
6–15	.....	..	5,900	39.3	10.6	1.0	0.3	..	1.3	47.3	0.3	..	301	Improving.
6–29	.....	..	4,400	24.7	7.0	2.0	1.6	..	2.0	61.5	0.6	0.3	299	Glands scarcely palpable.
9–15	3,990,000	85	5,800	11.7	3.9	0.6	0.3	..	0.6	81.4	1.0	0.3	307	Gained 15 pounds; lower cervical and axillary glands palpable.

The blood Wassermann, tuberculosis complement-fixation and Widal tests were negative. Stool cultures were negative for typhoid group of organisms. The phenolsulphonephthalein renal function test was 64 per cent in two hours. A biopsy examination of a lymph node from the left axilla showed central destruction of normal structures with lymphoid and endothelial proliferation, not pathognomonic of any disease known to the pathologist. No malarial parasites were found. There were a few elongated and rather crescent-shaped red blood corpuscles. The abnormal lymphocytes varied in size up to that of the large mononuclear cell. These cells had the "blue ground-glass" appearing cytoplasm, which was ragged in outline in some of the smaller cells. The cells were considered typical of infectious mononucleosis. The platelets were normal in appearance.

CASE VI.—*Infectious Mononucleosis Complicating Chronic Duodenal Ulcer.* G. L. S., white, male, aged fifty-one years, executive, married, was admitted June 22, 1925, complaining of vomiting of blood and soreness in the lower abdomen. The past history was irrelevant excepting that for thirty years he has had recurrences of a duodenal ulcer. Fifteen years before he went on a Sippy diet and remained free from pain for eight months. Since then he has been on alkalis and laxatives. One year before he had had hematemesis and was confined to bed for three weeks. The pain disappeared, but returned two weeks before admission to the hospital. At this time, he again had a small hemorrhage with nausea and vomiting. One week before admission he noticed that the cervical lymph nodes were enlarged enough so that he could see them in the mirror. The throat was not acutely inflamed but felt uncomfortable and sore. Urticaria appeared on the hands and feet.

The tongue was furrowed and coated. The cervical, postauricular, supraclavicular and inguinal lymph nodes were discretely enlarged, firm, but not tender. The blood pressure was 100 systolic and 60 diastolic. There was tenderness along the transverse and descending colon and in the epigastrium at the right of the midline. The spleen was enlarged to percussion but not palpable. The blood Wassermann was negative. The nonprotein nitrogen was 25 mg. The gastric analysis showed a coffee-groundlike substance. The free hydrochloric acid was 10 and the total acidity was 40. The Dock test meal showed mucus and positive benzidin blood test. The stools were reported normal. A gastrointestinal fluoroscopic examination showed a deformed duodenal cap, colonic motor delay and redundancy. The urine contained a trace of albumin. The throat culture was negative for spirochetes and contained Streptococcus hemolyticus and Micrococcus catarrhalis.

The gastrointestinal condition was treated and the patient began to improve. The lymph nodes soon began to diminish in size and were not palpable after about a month. The mononucleosis was apparently coincident with the gastrointestinal relapse. While under observation, the temperature rose to 37.8° on two occasions. After about the twelfth day of the disease he no longer showed any remarkable temperature elevations. Eighteen months later he reported himself as well in all respects.

CASE VII.—*A Case with Symptoms of Acute Appendicitis.* S. G. B., white, aged fifty-six years, male, single, was admitted to the Missouri Pacific Hospital, September 29, 1924, on the service of Dr. W. B. Elmer, to whom I am indebted for permission to report this case. The patient complained of pain in the right lower abdomen. As an adult, he had frequent attacks of tonsillitis and rheumatic pains. Hay fever occurred during the summer. The only gastrointestinal complaints had been constipation. At times, he had slight dizziness and head noises. The morning of admission he became suddenly ill with severe pain in the right abdomen. Nausea

and vomiting occurred and an icebag was applied to the right side to relieve pain. The pain remained severe until about 3 P.M.

Examination revealed a fairly well-nourished, rather pale individual in only slight discomfort. Teeth had suspicious caries, the throat showed slight congestion. The thyroid and the cervical lymph nodes were not enlarged. The abdomen was full, without rigidity, but was slightly tender over the cecum. The inguinal glands were enlarged.

The first and second day the temperature reached 37.4° and 37.2°; all other temperature readings ranged from 37° or below. It was the impression of the physicians who saw him that he was suffering from appendicitis until after a blood examination was made.

The urine contained a slight trace of albumin, a few leukocytes, and an occasional red blood cell. Two examinations of the sputum for acid-fast organisms were negative. The Roentgen ray of the chest showed no evidence of tuberculosis. The patient improved rapidly and was permitted to go home on October 10, 1925.

The blood smears were submitted to me for diagnosis. The abnormal lymphocytes were characteristic. I was permitted to see the patient several weeks after discharge. He was feeling well but still had the abnormal cells in the blood and the lymph nodes were still enlarged. He was reported well a year later. At the time of his discharge from the hospital it was considered possible that the appendiceal symptoms had been caused by local involvement of the lymphoid structures as a part of a general lymphadenopathy.

TABLE VII.—BLOOD FINDINGS OF S. G. B.

Date.	R. B. C.	W. B. C.	Hgb.	Differential.		
				Small lymphocytes.	Large lymphocytes.	Neutrophils.
9–30–25	.....	30,000	....	65	11	22
10– 1–25	4,660,000	31,600	123	75	5	20
10– 3–25	.....	26,650				
10–10–25	.....	25,800				

TABLE VIII.—BLOOD FINDINGS OF E. G. A.

Date.	R. B. C.	W.B.C.	Hgb. (%).	Neutrophils.	Eosinophils.	Basophils.	Transitionals.	Large lymphocytes.	Small lymphocytes.
1–25–26	4,760,000	7,600	84 (D)	32.0	0	0.5	1.0	0	65.0
1–26–26	.....	6,700	...	..	0.06	0.5	0.5	1.4	588.0
1–27–26	4,358,000	7,300	79 (N)	56.5	1.40	...	...	1.4	40.4
1–28–26	.....	8,400	...	50.3	..	0.6	1.0	4.5	43.6
									30.0*
1–24–26	.....	...	...	34.0	2.00	1.0	5.0	..	22.0
									43.0
1–30–26	.....	2,000	...	36.5	1.00	0.5	2.0	?	12.5
2 –1–26	.....	7,800	...	45.5	1.00	...	2.0	..	51.5
2– 2–26	.....	7,600	...	44.9	..	1.3	2.3	..	50.3
2– 4–26	.....	7,300	...	42.8	..	...	5.3	0.8	51.1
4–22–27	.....	...	...	40.3	1.40	...	1.8	6.2	34.1
								72.0	9.1*

* Abnormal.

TABLE IX.—BLOOD FINDINGS IN THE CASE OF E. M.

Date.	R. B. C.	W.B.C.	Hgb. (%).	Differential in percentage.										Remarks.	
				Neutrophils.	Eosinophils.	Basophils.	Transitionals.	Large mononucleears.	Large lymphocytes.		Small lymphocytes.		Myelocytes.	Spleen.	Lymph nodes.
									Normal.	Abnormal.	Normal.	Abnormal.			
10- 7-25	4,700,000	8,000	84												
9- 3-26	.....	..	..	30.0	..	..	3.0	16.0?	?	?	51.0				
8-11-26	.....	3,000	..	67.0	1.0	..	..	32.0	?	?	?	?			
9-17-26	.....	6,000	..	32.0	2.0	0.5	..	2.5	2.0	?	47.0	14.0?	..	Palpable	Post-auricular and cervical and right axillary.
10- 8-26	4,100,000	4,700	63 N	62.0	5.0	..	2.5	..	1.0	7.5	14.0	9.5	0.5	Palpable	Lymph nodes palpable; Türck cells.
10-25-26	4,900,000	6,300	62 N	52.0	1.0	2.0	1.0	1.0	4.0	5.0	16.0	18.0	..	Palpable	Palpable; Türck cells.
11- 8-26	5,450,000	6,400	75 N	67.8	2.6	..	4.0	0.8	4.4	0.4	14.0	5.3	..	Palpable (smaller)	Palpable.
11-24-26	5,020,000	6,840	75 N	50.0	1.0	..	2.0	2.0	7.0	2.0	26.0	11.0	..	Palpable (smaller)	1 tailed, 1 normoblast.
12-15-26	5,490,000	8,400	70 N	..	..	..	..	..	..	..	..	..	..	Smaller	Lymph glands not palpable.
2- 1-27	4,810,000	6,300	64 N	77.4	0.9	..	0.9	..	1.4	1.8	9.9	7.5	..	Smaller	Lymph glands not palpable.
3- 1-27	5,290,000	7,600	85 N	74.1	2.0	..	..	..	..	..	10.2	5.3	..	Not palpable	Not palpable.
6- 3-27	4,210,000	6,800	86	64.3	3.1	2.6	4.0	1.3	3.1	4.0	10.7	0.5?			

CASE VIII.—*An Infection of Insidious Onset Diagnosed by Blood Examination.* E. G. A., aged twenty-three years, male, white, medical student, was admitted January 24, 1926. About two weeks before admission general weakness and malaise began. During the three or four days before admission, he became worse, with afternoon temperature up to 38.4° to 38.6°, accompanied by chilly sensations, sweats, pain in the back and anorexia. He had lost 9 pounds. Constipation had been marked since the onset, and he had taken purgatives. There was no cough or sore throat. However, soreness had been present in the front of the chest.

Examination revealed slight tenderness in the right upper quadrant of the abdomen. Temperature varied from normal to 38.4°, but in general with gradual reductions in the afternoon. Slight fever was present until the time of his discharge. After a day or two the liver and spleen were enlarged to palpation and percussion for two to three days. On two occasions the patient vomited after slight exertion. The gastrointestinal fluoroscopic examination was negative except for slight colonic retardation. The Roentgen ray of the chest showed bilateral hilum enlargement. The phenolsulphonephthalein renal function test was 45 per cent in two hours. The blood culture and Widal were negative. Nine of 13 specimens of urine had traces of albumin or occasional casts, but chemical tests were negative for blood.

CASE IX.—*A Middle-aged Woman Suspected of Early Hodgkin's Disease.* E. M., aged forty years, female, housewife, came in October, 1926, for observation of blood condition. In 1911, when she had an examination resulting in a diagnosis of neurasthenia, constipation and nephritis, an unusually complete examination revealed no enlargement of the spleen, liver or lymph glands. In 1925, a diagnosis of cholelithiasis and of redundant and spastic colon was made. In April, 1925, a cholecystectomy was done without complications.

The present trouble began while she was away from home. In August she contracted a mild upper respiratory infection. The cervical and right axillary lymph nodes were enlarged. The spleen was palpable 3 to 4 cm. below the costal margin. There was a leukopenia and 67 per cent of the differential count consisted of mononuclear cells. At this time she was suspected of early leukemia. The Widal test was negative. A low-grade fever persisted for a little over one week. A week later a few râles were discovered at the right apex. Vague abdominal symptoms persisted and five weeks from the onset a gastrointestinal Roentgen ray series was made. No noteworthy abnormalities were discovered except a visceroptosis. The hilum glands of the lungs were enlarged and there were a few calcified nodules in both apices. The patient continued to have the vague abdominal symptoms and constipation. She was referred by a most competent physician for observation as a possible case of Hodgkin's disease. In October, she was put on a high-caloric diet, including generous daily portions of cooked liver. The data in the table indicate the general improvement since this corresponded to the improvement in the blood picture.

Discussion. Since attention has been directed to the blood findings of glandular fever and its apparent identity with infectious mononucleosis a rapidly increasing number of reports has been made of epidemics and its sporadic occurrence. The number of reports from so many widely separated sources indicates that the disease is not uncommon. Undoubtedly many cases are unrecognized if one can judge from the fact that only 1 of the above reported cases was found among 12,000 personally inspected medical histories.

The difficulties of diagnosis are fairly represented by this series of sporadic cases. It is especially important when the differentiation from leukemia is to be made. A mistake may cause much unnecessary anguish to the patient and embarrassment to the physician. The disease may also be confused with syphilis, tuberculosis and Hodgkin's disease. It is also of considerable interest that patients may have confusing abdominal symptoms.

The diagnosis cannot at present be made without repeated blood counts and very careful differential count. In some instances, the suspicion of leukemia may persist even after several such examinations.

Previous reports, as illustrated by several of our cases, show that the abnormal cells may persist in the blood of the patients for months or years after the initial infection, and be a source of confusion during subsequent sickness unless the knowledge of the previous infection is known.

Conclusions. Nine cases of sporadic infectious mononucleosis (glandular fever) have been described with reference to their clinical pictures, the difficulty and importance of their diagnosis.

The diagnosis can only be established by a careful study of the differential white blood cells in association with clinical features.

Symptoms may persist for a few months but the abnormal blood picture may persist for months or years after the initial attack.

Patients may be affected in the fourth of fifth decades as well as during childhood and early adult life.

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REVIEWS.

POLIOMYELITIS. By W. RUSSELL MACAUSLAND, M.D., Surgeon in Chief to the Orthopedic Dispensary of the Carney Hospital, Boston, Mass. Pp. 402; 173 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $5.50.

THIS is a well-written and elaborate résumé of what is known or admitted regarding this most frequent cause of acquired deformities and of the best methods of treatment used by experienced orthopedic surgeons in the prevention and correction of the resulting deformities. It is well and logically presented and great care has been shown in the selection of the best from the extensive literature. He has brought together most advantageously the principles he has proven in his treatment of these cases though nothing new is presented. He stresses a most important point commonly lost sight of by many medical men and by the laity, viz.; that the disease affects chiefly the motor cells in the cord and the paralysis is but the result. Muscle fatigue or palsy is but the peripheral expression of the state of the motor cells and therefore too early attempts to restore function and control of the muscles tend to increase motor cell degeneration. In the correction of several of the foot deformities, the author's enthusiastic advocacy and performance of astragalectomy (after Whitman) will be challenged by many of the more conservative but successful operators. The illustrations are clear and descriptive, typographical errors are few and the book can be recommended to the practitioner who is seeking an epitome of the orthopedic world's best presentation in this most interesting though most disastrous of diseases. J. R.

THE FOUNDATION OF HEALTH. A MANUAL OF PERSONAL HYGIENE FOR STUDENTS. By WILLIAM BARNARD SHARP, S.M., M.D., PH.D., Professor of Bacteriology and Preventive Medicine in the Medical Department of the University of Texas. Second edition. Pp. 288; 20 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $2.50.

THIS book has been planned for use in teaching hygiene in colleges, whether they be taking premedical work or not. The material is well presented; concise but adequate. At the end of each chapter are references for more extensive reading. R. K.

THE OPHTHALMIC YEAR BOOK. VOL. XXIII. Edited by WILLIAM H. CRISP. Pp. 338. Chicago: Ophthalmic Publishing Company, 1927.

THE volume for 1927 brings the literature up through December, 1926. It has maintained its high standard of former years, and the arrangement of topics with their short abstracts makes it a valuable reference book.

The subject matter is arranged as near as possible under anatomic headings, and besides the general index at the beginning, each chapter commences with a list of the topics to be discussed. H. S.

HEALTHY GROWTH. By A. A. MUMFORD, Medical Officer to Manchester Grammar School. Pp. 348; 28 illustrations. New York: Oxford University Press, American Branch, 1927.

AN interesting presentation is given of the physical measurements of boys attending an English Grammar School (a school drawing boys from mixed sources) in relation to mental progress. Efficient development of respiratory power is associated with rapid mental progress, but physical development in this and other ways is retarded at time of examination stress. H. B.

CLINICAL CASE-TAKING SUPPLEMENT TO METHODS IN MEDICINE. By GEORGE R. HERRMANN, M.D., PH.D., Assistant Professor of Medicine, Tulane University, New Orleans. First edition. Pp. 78. An Appendix with 8 Anatomical Outlines for Diagramming Regional Abnormalities. St. Louis: The C. V. Mosby Company, 1927. Price, $1.50

WHILE Dr. Herrmann was at Ann Arbor in 1924 he had published a volume entitled, "Methods in Medicine, the Manual of the Service of George Dock." This book is a very complete guide for the conduct of a hospital medical service except that the chapter on History Taking and Physical Examination was written rather briefly. The author did this presumably out of deference to his former chief, Dr. Dock, who had published at the time a third edition of his "Outlines for Case Taking."

"Clinical Case Taking" now is written by Dr. Herrmann to supply what he evidently must himself have thought to be a weak feature in his first book. It is rather fortunate in a way because it has made for a smaller, more convenient book to carry to the bedside of the patient. It is the best book of the kind we have seen. We agree with the author that although it sets a goal for student, interne

and practioner difficult of achievement, yet it is for this very reason most desirable. Using it as a continual working guide in the study of patients, the user should develop at least to a high degree of perfection in the art of diagnosis and therefore in the art of treatment. It would be difficult to make any adverse criticism of the book from its very happy dedication to the well-done index.

T. S.

THE QUEEN CHARLOTTE'S PRACTICE OF OBSTETRICS. By J. BRIGHT BANISTER, M.D., F.R.C.S., Obstetric Physician, Charing Cross Hospital, ALECK W. BOURNE, M.D., F.R.C.S., Obstetric Surgeon to Out-Patients, St. Mary's Hospital, TREVOR B. DAVIES, M.D., F.R.C.S., Gynecological Surgeon, Hospital for Women, Soho, L. CARNAC RIVETT, M.C., F.R.C.S., Surgeon, Chelsea Hospital for Women, L. G. PHILLIPS, M.S., F.R.C.S., Assistant Surgeon, Hospital for Women, Soho, C. S. LANE-ROBERTS, M.S., F.R.C.S., Obstetric Surgeon, Royal Northern Hospital. Pp. 605; 270 illustrations. New York: William Wood & Co., 1927. Price, $7.00.

THIS presentation represents the combined work of the above-named members of the staff of this ancient lying-in hospital, a short history of which opens the text. That the methods of the hospital are as modern and progressive as any may be seen from a reading of the text and a perusal of the statistics given in some of the final chapters.

The book is well balanced, the ideas advocated safe and conservative, considering the multiplicity of authors there is a marked absence of controversial discussion. The hospital technique as described is that of a modern aseptic harmonious surgical team. It may be noted that the Kjelland forceps are not well known in England, that the low cervical section is not practised at the Queen Charlotte Maternity Hospital and that great faith is laid upon the intravenous use of arsenicals in the treatment of streptococcal blood-stream infection in the puerperium. There are several excellent chapters as addenda, Fetal and Maternal Mortality, Fetal Morbidity, Pituitrin, Anesthesia, Roentgen-rays, etc.

For the use of a student or practitioner the volume may be highly commended.

P. W.

ATLAS THORACOSCOPICON. By DR. FELIX COVA. Pp. 50; 50 illustrations. Milan: Sperling and Kupfer, 1927. Price, $9.00.

APPARENTLY the first atlas of its kind in any language, this well-prepared book presents 50 colored reproductions, with text in Italian, German and English. All but 3 of the excellent plates are round

trichromes, imitating the thoracoscopic field, with a segment of the parietal pleura in the upper half and of the lung in the lower. Aside from a tendency to be too diagrammatic and vivid—"fibrinous pleurisy" might easily pass for an Aurora borealis in the far north—the plates are well done and should be useful to students of this field. The polyglot text, too has its uses. Those who wish to brush up their medical Italian and German have a context close at hand—in fact, they are even stimulated to use them by the grotesqueness of the English translation. Misspelling, solecisms and grammatical faults to the extent that are here found are inexcusable in any scientific publication, no matter how polyglot. E. K.

EMERGENCIES OF A GENERAL PRACTICE. By NATHAN CLARK MORSE, A.B., M.D., F.A.C.S. Revised and rewritten by AMOS WATSON COLCORD, M.D., Surgeon, Carnegie Steel Company. Second edition. Pp. 541; 311 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, $10.00.

COLCORD's revision of Morse's book, appearing nine years after the publication of the first edition, has been thorough. Much has been omitted, much added to bring it up to date. While the work makes no pretension to originality, it has the virtue of including in a single volume material otherwise obtainable only from many. It is clear and practical, and should be of value to the industrial surgeon, the rural doctor and the general practitioner. The scope of the work is great, ranging from insect stings to major surgical and obstetrical emergencies. The chapter on fractures is especially valuable. R. G.

OPHTHALMOSCOPY, RETINOSCOPY AND REFRACTION. By W. A. FISHER, M.D., F.A.C.S. Second revised and enlarged edition. Pp. 291; 260 illustrations. Philadelphia: F. A. Davis Company, 1927. Price, $3.75.

THE second edition of this book is somewhat improved over the first by the addition of a small chapter by Dr. Robert von der Heydt on the newer methods of ophthalmic diagnosis. In general, however, the book remains as poor as the first edition. F. A.

AN INTRODUCTION TO CLINICAL PERIMETRY. By H. M. TRAQUAIR, M.D., F.R.C.S., ED. Pp. 264; 165 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, $13.50.

THIS volume is the most comprehensive both in quality and quantity, that has yet been published on the subject. It is an

"amplification of the Meddlemore Essay for 1920 on Perimetry, Its Methods and Its Value to the Ophthalmic Surgeon."

There are 164 excellent illustrations with one colored plate of the optic pathways.

In regard to the methods of field testing, the author has described and explained a procedure which he and others have found easy, adequate and satisfactory. It is known as the quantitative method of perimetry, which is practically that of Bjerrum.

The anatomy of the visual path has been stressed and some mention of pathological conditions has been made in order to make the reader better understand the alterations in function, and changes in visual fields.

This is a book that should be in every ophthalmologist's library.

H. S.

EPIDEMIC ENCEPHALITIS (ENCEPHALO-MYELITIS). By LEO M. CRAFTS, B.L., M.D., Formerly Dean and Professor of Nervous and Mental Diseases, Hamline University, Minneapolis, Minnesota. Pp. 237; 15 illustrations, and 52 case reports. Boston: Richard G. Badger, The Gorham Press, 1927.

THE project here on foot, to give a comprehensive treatise in language that is simple, is for the most part successful, especially in point of language.

Diagnosis is particularly inclusive with its more than thirty subject-heads, and noteworthy is that entitled simulated surgical states.

In the preface some weakness is shown where a fling is taken at the psychoanalysts, and in treatment, where their success is not even mentioned. Again, one observes failure to describe that type of patient, who some time after subsidence of active symptoms, shows delinquencies, to which previous to his illness he was a stranger.

N. Y.

LABORATORY MANUAL OF ORGANIC CHEMISTRY FOR STUDENTS OF THE MEDICAL SCIENCES. By HUGH C. MULDOON, D.Sc., Prof. of Chemistry and Dean of the School of Pharmacy, Duquesne University, Pittsburgh. Pp. 118; 8 illustrations. Philadelphia: P. Blakiston's Son and Co., 1927.

THIS manual describes the preparations of about forty organic compounds of different types, and outlines qualitative tests by means of which some of their properties are determined. In addition, tests to determine characteristic properties of a number of naturally occurring fats, oils and alkaloids are outlined. Chemical equations and formulas are omitted, as are practically all considerations of reaction velocities and equilibria. No mention is made of

the ampholytic nature of most of the compounds which are of interest to the student of medical sciences. A few chapters, such as those which deal with proteins and alkaloids emphasize precipitation reactions and color tests rather than transformations of definite chemical groups. The manual gives numerous references to the text for which it was designed, and contains only a few errors of print. W. L.

MANUAL OF THE DISEASES OF THE EYE FOR THE STUDENT AND GENERAL PRACTIONER. By CHARLES H. MAY. Twelfth edition, revised. Pp. 445; 374 original illustrations, including 23 plates and 73 colored figures. New York: William Wood & Co., 1927. Price, $4.00.

THERE have been no important changes in the twelfth edition of this valuable manual. It continues to be the best available outline of ophthalmology for the undergraduate student. F. A.

NOMOGENESIS OR EVOLUTION DETERMINED BY LAW. By LEO S. BERG, Chief of the Bureau of Applied Ichthyology and Professor of Geography in the State University of Liningrad. Translated from the Russian by J. N. ROSTOVTSOW. Introduction by D'Arcy W. Thompson. Pp. 477; 33 illustrations. New York: Oxford University Press, 1926. Price, $10.00.

THIS work by a distinguished Russian student of fishes deals with a theory or explanation of evolution called in this country orthogenesis. In this theory there is no place left for chance; the course of evolution being fixed and predetermined. Although it is a theory with which few biologists will agree, yet as D'Arcy W. Thompson states in the introduction "the author is so modest, so candid, so careless of credit and priority that we may differ from him and yet be friends." The author has followed closely the work of American zoölogists and presents much recent Russian work with which American students should be familiar. The work is so well translated into idiomatic English that one is not conscious of its foreign source. The bookwork is excellent and the bibliography full, containing over four hundred references.

H. C.

MINOR SURGERY. By ARTHUR E. HERTZLER, M.D., F.A.C.S. and VICTOR E. CHESKY, A.B., M.D., F.A.C.S. Pp. 568; 438 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, $10.00.

THIS book, as stated by the writers, is written primarily for use by the young surgeon and the interne. The data given is that which

has stood the test of time and no treatment is mentioned that has not been proven efficacious. In other words, all statements are made of a positive nature and no theories or surmises are considered. The work is best from the standpoint of diagnosis. The many illustrations, some of which are of rather unusual conditions, enhance its value to a great extent. The treatment of the various conditions is clearly outlined although minor surgical technique as such takes a secondary position.

The book is well written, of convenient size, well made from the standpoint of binding and as a diagnostic and treatment outline it fills a distinct place in literature. E. E.

BOOKS RECEIVED.

New Books.

*The Polynuclear Count.** By W. E. Cooke and Eric Ponder. Pp. 79; 25 illustrations. Philadelphia: J. B. Lippincott Company, 1928. Price, $3.00.

*The Examination of the Central Nervous System.** By Donald Core, M.D., F.R.C.P. (Lond.). Pp. 248; 14 illustrations. New York: William Wood & Co., 1928.

Bacteriology and Surgery of Chronic Arthritis and Rheumatism. By H. Warren Crowe, D.M., B.Ch. (Oxon.), M.R.C.S. Pp. 187; 40 illustrations. New York: Oxford University Press, American Branch, 1928. Price, $9.00. A high-priced supplement to the author's "Treatment of Chronic Arthritis and Rheumatism" with a special plea for the pathogenicity of some S. albi (M. deformans).

Modern Baking Powder. By Juanita E. Darrah, A.B., A.M. Pp. 125; illustrated. Chicago: Commonwealth Press, Inc., 1928. Price, $1.00.

*Animal Biology.** By J. B. S. Haldane and Julian Huxley. Pp. 344, 122 illustrations. New York: Oxford University Press, 1927. Price, $2.50.

*The Harvey Lectures, 1926–1927. Series XXII.** By Fred. Neufeld, Robert Chambers, Leonor Michaelis, Joseph Erlanger, Edgar L. Collis, Richard Willstätter, Merkel H. Jacobs. Pp. 164. Baltimore: Williams & Wilkins Company, 1928.

*Percival's Medical Ethics.** By CHAUNCEY D. LEAKE. Pp. 290; 10 illustrations Baltimore: Williams & Wilkins Company, 1928. Price, $3.00.

Medical Clinics of North America, Brooklyn Number, January, 1928. Pp. 277; 53 illustrations. Philadelphia: W. B. Saunders Company, 1928.

Systemic and Focal Immunization through Irradiation. By S. PESKIND. Pp. 30.

*Recent Advances in Tropical Medicine.** By SIR LEONARD ROGERS. Pp. 398; 12 illustrations. Philadelphia: P. Blakiston's Son & Co., 1928. Price, $3.50.

Surgical Clinics of North America. Lahey Clinic Number, February, 1928. Pp. 210; 74 illustrations. Philadelphia: W. B. Saunders Company, 1928.

*Crawford W. Long and the Discovery of Ether Anesthesia.** By FRANCES LONG TAYLOR. Pp. 237; 8 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $4.00.

Diagnosis and Treatment in Diseases of the Lungs. By FRANK E. TYLECOTE, M.D., D.P.H. (VICT.) and GEORGE FLETCHER, M.A., M.D. (GLAS.). Pp. 270. New York: Oxford University Press, American Branch, 1928. Price, $2.25. A handy volume for "the senior student or the young practitioner" who realizes its limitations.

New Editions.

*The Mechanics of the Digestive Tract.** By WALTER C. ALVAREZ, M.D. Second edition. Pp. 447; 100 illustrations. New York: Paul B. Hoeber, Inc., 1928 Price, $7.50.

*The Theory of Emulsions and their Technical Treatment.** By WILLIAM CLAYTON, D.Sc., F.I.G. Second edition. Pp. 283; 42 illustrations. Philadelphia: P. Blakiston's Son & Co., 1928. Price, $4.50.

Clinical Researches in Acute Abdominal Disease. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.). Second edition. Pp. 214; 44 illustrations. New York: Oxford University Press, American Branch, 1928. Price, $3.50.

The Pneumothorax and Surgical Treatment of Pulmonary Tuberculosis. By CLIVE RIVIERE, M.D. (LOND.), F.R.C.P. Second edition. Pp. 311; 25 illustrations. New York: Oxford University Press, American Branch, 1928. Price, $3.25.

Postmortems and Morbid Anatomy. By THEODORE SHENNAN, M.D., F.R.C.S. (EDIN.). Second edition. Pp. 664; 214 illustrations. London: The Scientific Press, 1928. "Multum in parvo" but hardly "quantum sufficit."

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,
PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Influence de l'Ingestion d'Albuminoides sur la Pression Artérielle.—PAGNIEZ and ESCALIER (*Presse méd.*, 1928, p. 1) record some observations they have made on individuals who have been given a meal rich in protein. Observing the blood pressure at intervals from ten to twenty minutes after the meal, they find that this protein seems to have a distinct depressing effect on blood pressure. In a normal individual it causes a fall in the blood pressure of 20 to 30 mm. of mercury. In individuals who have hypertension an even greater fall follows excessive protein intake. They record one case, for example, whose pressure fell 40 mm. of mercury systolic and 20 diastolic. They call attention to the importance of this observation in that in examining a patient inquiry should be made into the time of the last meal and the character of the meal, as otherwise figures may be obtained which are not truly indicative of the pressure for that individual.

Effect of Kidney on Blood Regeneration in Pernicious Anemia.—It is only to be expected that following the remarkable improvement of patients with severe anemia following the ingestion of large quantities of liver, as suggested experimentally by Whipple and clinically by Minot and Murphy, other parenchymatous organs should be utilized to study their effect on blood regenerations. This has been done by MCCANN (*Proc. Soc. Exper. Biol. and Med.*, 1928, **15**, 255) who reports on 2 cases of pernicious anemia who were fed diets containing 250 gm. of kidney daily without other foods of high value in blood regeneration. The response to this dietary was as spectacular as is the response to liver diet. In the first case the red blood count rose in seventeen days from 1,400,000 to 2,600,000 and the hemoglobin from 45 to 74 per cent. In the second case, in a period of twenty-seven days, the red cell count increased from 2,200,000 to 3,800,000 and the hemoglobin from 69 to 75 per cent. In both cases there was a marked increase in the percentage of reticulocytes. This observation of the author is interesting. It is quite possible that if kidney also causes remissions, it cannot be said that the liver feeding, whether in the form of the whole gland or in extract, can be said to be specific.

On The Specificity of Scarlet Fever Streptococci.—It has been quite generally felt by the general medical profession that the hemolytic streptococcus responsible for scarlet fever is a specific organism, which, likewise, holds true of other infectious diseases, such as erysipelas and puerperal fever. The specificity of these organisms, however, has been doubted by many bacteriologists. From Ukraine comes an expression of doubt which seems to be confirmed by the experimental work carried out by ZLATOGOROFF and DERKATCH (*J. Infect. Dis.*, 1928, **42**, 56). They show that the streptococci from nonscarlet fever series produced toxins which give a skin reaction of the Dick type under the same conditions as do the same types of scarlet fever streptococci. The positive reaction of Dick during the course of the complications of scarlet fever may be obtained with many types of streptococci. The phenomenon of extinction, commonly called the Schultz-Charlton reaction, may be obtained by immunization with diverse types of streptococci. These authors conclude that toxin production with the Schultz-Charlton reaction does not permit the confirmation of the specificity of the scarlet fever streptococci.

A Note on Difficulty of Turning Over in Bed.—The great clinicians of the past depended largely on the keen power of observation and their skill in deduction from what they observed in order to make a diagnosis. This often was apparently brilliant in the extreme, but in reality depended upon the noting of some apparently trivial event in in the course of the disease or some unusual feature in the examination of the patient. BLUMER (*Boston Med. and Surg. J.*, 1928, **197**, 1260) contributes a note on an observation he made which has apparently escaped other clinicians. He has seen patients with hidden carcinoma who have involvement of the spinal column expressing marked inability of discomfort in moving in bed. Hidden carcinoma frequently is in the prostate gland. Therefore, individuals who present this symptom, together with the symptoms of malignancy, should have a prostatic examination.

Systolic Blood Pressure in Cardiac Decompensation and During Compensation.—For some peculiar reason it is very generally held that during cardiac failure the systolic blood pressure falls and that as it rises compensation is restored. The error of this supposition seems to depend upon faulty reasoning and not upon critical observation. Anyone who has followed these decompensated patients with daily blood-pressure observations appreciates the fact that restoration of compensation is followed by a fall in the blood pressure. This was pointed out by German observers twenty-five years ago. The paper of MEYER and MULLEN (*Am. Heart J.*, 1928, **3**, 356) again calls attention to this phenomenon which they observed in 45.7 per cent of 35 cases of congestive heart failure, the pressure falling from 10 to 40 mm. of mercury as compensation was restored. The authors discuss briefly the possibilities which have been suggested to explain this fact, which usually has been held to be due to increased CO_2 content of the blood. They point out, rightly, that cyanosis is infrequent in aortic disease and, therefore, this basis does not explain the rise in blood pressure in this particular type of valvular lesion. They suggest, rather, that it is a combination of mechanical factors and increased tonus of the vasomotor center which together bring about an increase in systolic pressure.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Pathology of the Thyroid Gland.—STRICKLER (*Kentucky Med. J.*, 1927, **25**, 229) says that fully 95 per cent of malignant growths of the thyroid gland are carcinomatous depending upon the fetal adenoma for their origin. Sarcomata represent the remaining 5 per cent of malignant cases. These sarcomata do not differ from sarcomata in other parts of the body. Their origin is the lymphoid tissue commonly present in thyroids. Fetal adenoma has its origin in the so-called Wolfer's rests, remnants left over from the developmental period of the thyroid gland. The usual site of these adenomas is in the lower pole of the right lobe, occasionally found in the isthmus, but may occur in any part of the gland. Adolescent goiter is a type which appears at a developmental period of life and disappears again. However, it sometimes continues to develop and assumes a definite pathological entity, which may be considered a simple colloid goiter. Diffuse adenomatous goiters are of two types, glandular and papillary. Both are toxic and there is no macroscopic difference between these types. They vary greatly in size. When small they may be firm and elastic; when large soft and pulsating. On section, they vary from red to grayish-red in color. In the glandular type the chief change is in the acinal cells. While in the papillary type there is a proliferation of the cells of the preëxisting acini producing projections of papillary formation into the lumen of the acini.

Septicemia.—COHN (*New Orleans Med. and Surg. J.*, 1927, **80**, 84) states that many attempts have been made to prove that cures in cases of septicemia have been due to the introduction of some chemical substances directly into the blood stream. This has been based on the belief that *in vivo* the action of the drug would be the same as *in vitro*. There is experimental proof that the maximal concentration advisable to introduce into the circulation has no bactericidal action. We, therefore, have little to expect in a direct curative way from intravenous chemical medication. The so-called specific action of the various dyestuff, presupposes a selective bacteriotropic action and a negative organotropic action. This, Dale, contends, we have no reason to believe, exists. Apparently the stimulating effect on the body cells by the drug injected has been overlooked. There is experimental evidence to prove that bacteria disappear soon from the blood stream and settle in the spleen, liver, bone marrow and lymph nodes. Positive blood cultures signify only that the organisms are being transported by the blood stream. It does not signify that multiplication takes place

in the blood stream. Multiplication takes place in the foci where the organisms settle out from the active circulation in the reticuloendothelial system. Phagocytosis is the special function of the cells of this system. The author strongly advocates blood transfusion to stimulate this potential defensive mechanism, namely, the reticuloendothelial system.

Hydrocele of the Tunica Vaginalis.—CAMPBELL (*Surg., Gynec. and Obst.*, 1927, **45**, 192) says that hydrocele is a relatively common condition and constitutes about 3.6 per cent of all urologic cases requiring hospital care. The etiology is undetermined in the majority of cases. However, infection and trauma are chief of the known causes. Probably painless subacute epididymitis (nonvenereal) is the underlying factor in a great number of instances. The condition is observed most frequently in young adults. In infancy it is usually congenital and associated with hernia. Acute hydrocele is usually symptomatic. Pain is the chief complaint. In the chronic type a sense of mass and weight is noted. Transillumination of a scrotal mass is pathognomonic of hydrocele. Differential diagnosis is extremely difficult at times. While simple tapping with or without injections of irritants relieves many, open operation, preferably excision and eversion of the sac is the procedure of choice. Local anesthesia is most satisfactory in these cases. Complication is not uncommon, loss of the testicle by infection being probably the most severe. Two patients in a large series of 500 cases died following treatment, both of bronchopneumonia. One of these deaths followed simple tapping without injection.

Carcinoma of the Rectum.—JONES (*J. Missouri State Med. Assn.*, 1927, **24**, 179) believes that the only symptoms which should be of especial interest to us are bleeding from the rectum and any change in the patient's bowel habit or sensations. These symptoms should lead to a positive diagnosis if there is a growth present anywhere in the rectum by digital examination or by the use of the proctoscope. There is no need whatever in seeking further for methods of diagnosis of carcinoma of the rectum. In fact, the author strongly believes that the Roentgen ray should not be used until after digital and proctoscopic examinations have been made, as it frequently errs in the diagnosis of carcinoma of the rectum and therefore tends to do harm rather than good. Little or nothing is known about the etiology of cancer in this location, a fact which holds for cancer in any location. The types of growth are adenocarcinoma, squamous cell and very rarely basal-cell carcinoma. While diagnosis of carcinoma of the rectum is still made very late, some progress has been made in standardizing the operations for this condition. The operative treatment may be divided into three periods: the first extending up to 1895, when little else than palliative operations were done; the second period from 1895 to 1912 when practically all operations were done by the posterior route and consisted of removing the growth and a small amount of intestine above it; in the third period from 1912 to date, the abdominoperineal operation has been struggling for recognition, in addition to the posterior operations. A full historic development and exposition of the need of radical lymphatic control is given in this excellent Hodgen lecture.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY.

An Improved Toxin-antitoxin for Diphtheria Immunization.—The improvements in the materials for protective inoculation against diphtheria, like those which have been made in the purification and concentration of the antitoxin may be expected to aid materially in the extension of effective prophylaxis to increasingly larger proportions of the susceptible population. In 1925 Schnidt and Scholz showed that a saline suspension of the floccular precipitate of a diphtheria toxin-antitoxin mixture was a very effective means of producing active immunity in animals. Now EBERHARD (*Deutsch. med. Wchnschr.*, 1928, **54**, 91) reports on the administration of this saline suspension, called T. A. F., to a series of 257 persons. The dose varied from 0.5 cc. for children to 1 cc. for adults, and the injection was strictly subcutaneous, except in a few instances in which the results of intramuscular inoculation were being investigated. It was found that a single inoculation was fully adequate to produce an effective immunity as determined both by the results of the Schick test and by determinations of the antitoxin content of the patients' blood sera. One week following the single dose the average antitoxic power of the serum was raised two and a half times. Frequently repeated titrations showed a progressive increase in antitoxin content of the serum, so that two months after the inoculation it was about sixty to seventy times the preinoculation level and one hundred to one hundred and ten times the normal at the fourth to sixth months. Neither local nor systemic reactions followed the subcutaneous injection, except occasional slight local redness and swelling. Intramuscular injection caused mild local tenderness and soreness only. The advantage of being able to produce rapid and effective immunity by a single nontoxic injection is considerable in older children and great in younger ones. The preparation is thoroughly tested for both toxicity and immunizing activity on guinea pigs. While it contains very little horse serum, enough is present to be capable of causing local reactions in sensitive individuals, although such reactions were not encountered by the author.

The Toxic Actions of Synthalin on the Liver.—While synthalin, a guanidin derivative, has been said repeatedly to be free from the toxic actions of guanidin when administered in doses sufficient to reduce the sugar content of the blood, many clinicians have found it to be decidedly toxic to man and its effective employment is often impossible on this account. Various authors are cited by HORNUNG (*Klin. Wchnschr.*, 1928, **7**, 69) as having observed during the clinical administration of

synthalin the occurrence of diminished tolerance for fat, increase in the amounts of urobilogen and urobilin in the urine, jaundice and swelling and tenderness of the liver. All of these phenomena suggest the occurrence of a toxic action of the preparation on the liver. The author, therefore, studied the effects of the prolonged administration of synthalin to dogs, with especial reference to its action on the liver. Ten to 30 mg. were administered daily by mouth, mixed with small amounts of food. The drug was omitted every third or fourth day. The general condition of the dogs rapidly became bad; appetite was much impaired, diarrhea developed, and frequent vomiting often interfered with the regular administration of the daily dose. All the dogs lost weight and strength and one died on the twenty-fourth day. All dogs ate better and appeared more normal on the days when no synthalin was given. Blood sugar was reduced by 11 to 44 per cent eight hours after doses of 10 to 30 mg., but hypoglycemic symptoms did not appear. The alkali reserve fell parallel with the level of the blood-sugar curve. Frequent determinations were made of the bilirubin content of the blood and of the gall-bladder bile. It was found to be increased from five to forty times in the bile, and was often increased in the blood, but this latter was neither constant nor very marked. Phenoltetrachlorphthalein tests regularly showed retention of the dye in the blood. After four weeks all dogs were killed, and in every one the liver was found to be in a state of marked toxic parenchymatous degeneration. The kidneys of one dog showed moderate parenchymatous degeneration, and in all animals the spleen showed increased pigmentation. The stomach, duodenum, gall bladder and pancreas showed no abnormalities. From these investigations the author concludes that in doses sufficient to lower blood-sugar synthalin is not only not indifferent, but is directly toxic to the animal organism. The toxic phenomena observed during the administration of synthalin to man are shown to be due to damage to the liver. In view of the production of both functional and structural changes in the liver, the prolonged clinical administration of synthalin demands the greatest caution. [Toxic action on the kidney has also been observed.—ED.]

The Effect of Liver and Iron on Hemoglobin Regeneration.—The problem of bringing about hemoglobin regeneration in the secondary anemias is an ever-present one, and information upon which rational therapy can be based must always be of value to the practitioner. RIECKER (*J. Clin. Invest.*, 1927, **5**, 141) reports a series of experiments carried out upon dogs which show results divergent from those reported by Whipple and his associates. Employing a carefully controlled technique, the author finds that the administration of liver exerts no specific action upon the regeneration of hemoglobin in adult dogs suffering from prolonged experimental anemia. Such action as liver does exert is brought about entirely by virtue of its iron content, and the feeding of liver fails to increase the production of red blood cells. Inorganic iron, on the other hand, in the form of Blaud's pills is found to supply utilizable iron, and to lead to effective regeneration of the hemoglobin in such animals. This regeneration under inorganic iron salts alone is found to be maximal, while under the administration of liver regeneration often proceeds at a slower rate.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Action of Ultraviolet Irradiation on the Bactericidal Property of the Blood.—GONCE and KASSOWITZ (*J. Am. Med. Assn.*, 1928, **90**, 280) made studies on the same therapeutic agent from a different aspect entirely. They found that the biologic action of ultraviolet rays on immunity might best be studied independently from other physical factors by using the artificial instead of solar radiation. The killing power of blood *in vitro* for certain test bacteria before and after general irradiation offers one criterion for the changes in the antibacterial properties that have taken place. Continuous daily quartz-lamp irradiations for more than four weeks with routine exposure time and distance lead, in the most of those cases examined, to a lowered bactericidal property of the blood. Completely normal persons free from infection are apt to show improved bactericidal properties after continuous ultraviolet irradiations. Those suffering from chronic infections and postinfections after daily quartz-light exposures are apt to show a drop in the bactericidal property of the blood. In tests on rabbits a very favorable response was shown to daily ultraviolet irradiations. The increased or reduced bactericidal property of blood after ultraviolet irradiation seemed to depend largely on the leukocytic reaction of the body. An increased number of white cells, especially of polymorphonuclears, was associated with improved destructive power for cocci, while a decrease showed a diminished destructive power. A comparative analysis between the number of leukocytes and the bactericidal property of the blood can be made in the same individual only at different times. Two different individuals may show the same numbers of leukocytes and the opposite bactericidal response, so that it must be assumed that there is comparatively high constancy in the bactericidal function of the single white cell in one individual, but differences in the leukocytic ability of different individuals. In managing the treatment the response of the organism should be controlled by the bactericidal test or, at least, by the leukocytic reaction of the blood. The white blood count should not be made immediately, but preferably twenty-four hours after a light treatment and not less than once a week. The borderline between the therapeutic and the toxic dose of ultraviolet rays with regards to immunity probably varies with each individual case.

Unilateral Symptoms in Meningitis.—LEVINSON (*J. Am. Med. Assn.*, 1928, **90**, 520) noted that unilateral manifestations may occur in meningitis. The unilateral symptoms may be intermittent or constant and may occur early or late in the course of the disease. This type of meningitis may occur in the infection with any form of bacteria. The postmortem in cases in which there have been unilateral symptoms may or may not show unilateral or localized pathology. Meningitis with uni-

lateral symptoms may be primary or secondary. Brain abscess, brain tumor, encephalitis and acute anterior poliomyelitis are the conditions most frequently confused with meningitis with unilateral symptoms. The examination of the cerebrospinal fluid is the best method of differentiation between meningitis with unilateral symptoms and other conditions. The treatment of a patient with meningitis of the unilateral type is either primary or secondary. In the secondary form attempt should be made to remove the original cause. In the primary form the cerebrospinal fluid should be examined in an attempt to find the causative organism, so that the serum may be used if it is a meningococcus meningitis or by palliative methods if other organisms are found.

The Penetration of Ultraviolet Rays into Live Animal Tissue.—MACHT, ANDERSON and BELL (*J. Am. Med. Assn.*, 1928, **90**, 161) studied the penetration of ultraviolet rays through animal tissue in two ways: In one method they used the spectograph, whil · in the other they used the thermopile. It was definitely established that penetration of the ultraviolet rays through the living skin and other tissues is much greater than has been heretofore suspected. Some of the shorter ultraviolet rays penetrate through the living skin more deeply than longer rays. A marked difference was noted between the living skin and the dead skin. White human skin is more penetrable to ultraviolet radiations than negro skin on account of the presence of pigment in the latter. The authors carefully checked and rechecked their observations, and their findings agree completely with the latest and most reliable clinical experience of other observers.

Celiac Disease.—SAUER (*Am. J. Dis. Child.*, 1927, **34**, 934) states that the celiac syndrome disappears when fresh cows' milk, carbohydrates and fats are omitted from the diet. The early or premature addition of these foods to the dietary is likely to provoke an exacerbation. Noxious intestinal products, probably formed by bacterial action on these substances, play an important part in the etiology. This disease has never been produced experimentally, but circumstantial evidence leads to the hypothesis that it might be transmitted from one child to another. This opinion of the author is entirely original. The prognosis depends on the diet rather than on the severity or duration of the disease. A standard, three-phased, high-protein diet yielded rapid and permanent results in a majority of the 25 patients for whom it was prescribed by the author during the past seven years. The first phase of the protein diet is the use of protein milk alone. This is usually continued until the patient has reached the best weight observed before the illness began. The second phase allows the addition of the following at the 10-A.M. and 6-P.M. feedings: Curd without whey, lean beef juice, cottage cheese, scraped beef and egg. The amounts of these additions are at first small and are then gradually increased. This stage may last many months or even years. During the third phase carbohydrates are added. Well-cooked meats, such as lean beef, mutton, chicken, fish and tongue, seem to be well tolerated if finely minced. Corn syrup, well-cooked cereals, such as rice, farina and arrow root, zwieback and well-cooked vegetables are cautiously added in slowly increasing amounts. Bread, potato, sugar, ice cream, candy, cake and

fresh milk should never be added during the first year, and preferably not until the end of the second year of the treatment. If there is a flare-up of the condition from any cause the first phase diet must be commenced again.

Blood and Cerebrospinal Fluid Sugar.—GRAYZEL and ORENT (*Am. J. Dis. Child.*, 1927, **34**, 1007) based their results upon the observations both of patients and experimental dogs. They found that the smallest variation in concentration of the sugar was obtained in patients who had not received food for ten hours or more. It fluctuated between 40.2 and 75.9 mg. per 100 cc., with an average content of the reducing substance of 61.7 mg. Experimental work on dogs showed that following the intake of glucose the sugar in the cerebrospinal fluid increased but after a fairly constant and comparatively long latent period. This increase was sustained for some time but the amount gradually returned to its previous level. The entire cycle occurred more rapidly than in the blood. The concentration of sugar both in the blood and in the cerebrospinal fluid was affected by the intake of glucose. There was no direct parallelism between the increase or decrease of sugar in the blood and in the cerebrospinal fluid. During the postabsorpt ve period there was a more definite correlation between the concentration of sugar in the blood and in the cerebrospinal fluid. During the absorptive period in the specimens of fluid obtained simultaneously the concentration of sugar in the whole blood and in the plasma may be equal to, greater than or less than that of the cerebrospinal fluid. In the postabsorptive stage the sugar content of the cerebrospinal fluid was always less than that of the blood or blood plasma. In order to place any diagnostic significance on the sugar content of the cerebrospinal fluid it must be on fluid obtained from a fasting person, preferably after a fast of ten hours or more.

Tubular Nephritis in Children.—DAVISON and SALINGER (*Johns Hopkins Hosp. Bull.*, 1927, **41**, 329) surveyed records of the Harriet Lane Home for the past fifteen years and among 53,965 sick children they found 26 cases that had been diagnosed as tubular nephritis or nephrosis. Six of the 20 patients about whom definite information was available were still well, and 5 of these have been well for more than seven years. Six of the 20 died. In 8 the disease is still active, although it cannot be said that they may not eventually recover. These cases indicated the reviewers that tubular nephritis or nephrosis is a clinical as well as a pathological entity, which can usually be recognized by its clinical course. The etiology is not now known. From these cases it would seem that the prognosis was more favorable than other reports would seem to indicate, although it must be emphasized that the duration may be long and that several years may elapse before the patient may be permanently free from edema and albuminuria. In those cases examined postmortem it was seen that the tubules of the kidney are more markedly involved than the glomeruli and interstitial tissue, although the latter are involved also. The authors feel that tubular nephritis is a better term than nephrosis, and that the presence or absence of hematuria and edema is most satisfactory means of classifying nephritis in children into its three principal anatomic varieties—glomerular, tubular and interstitial.

Birth Crisis in the Blood Picture of the Newborn.—BUNGELER and SCHWARTZ (*München. med. Wchnschr.*, 1927, **74**, 1822) observed that a direct relation existed between the length and difficulty of the birth and the degree of blood changes. They feel that the blood crisis in the newborn is caused by resorption of masses of blood and protein, which originate in birth traumas. In a series of infants, full-term and premature, the blood of the umbilical cord, obtained at the moment of birth, corresponded morphologically to that of adults. A storage of iron pigment by the reticuloendothelial system was noted in both full-term and premature infants. This storage began after birth and reached its height at the end of about two months. In degree it corresponded to the amount of blood destruction at birth.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Present State of the Knowledge of the Modern Chemotherapy of Syphilis.—LEVADITI (*Acta dermat.-ven.*, 1926, **7**, 201), before the Medical Society of Sweden, reviewed by invitation the recent progress in the treatment of syphilis. The article is of particular interest because of its review from the French standpoint of the therapeutic use of stovarsol. After citing the favorable reports of himself and his collaborators and of Fournier following the administration of the drug by mouth, he cites the work of Oppenheim, of Heymann and of Weitgasser in Germany. Oppenheim concludes that in doses of 0.25 gm. the drug has a definite, favorable influence almost equal to that of mercury, bismuth or arsphenamin upon the course of syphilis. He believes relapse to be infrequent and tonic effects to be marked, relapse occurring in only 2 out of 83 treated cases. The spirochete disappears from the lesion in twenty-four to forty-eight hours, the primary lesions healing in from five to fifteen days. Heymann found that in a daily dose of 1 gm. and a total dosage of 20 gm. the drug was well tolerated. He regards it as the most active form of treatment which can be administered by mouth and believes that it can be combined with other forms of treatment with safety. Weitgasser, on the other hand, takes a more conservative viewpoint and is correspondingly briefly reviewed by the author. In yaws 8 gm., in 1-gm. daily doses, apparently produces a cure in adults. Ravaut, Marchoux and a number of other

authors are quoted on the effect of the drug in amebic dysentery and lamblia infections. A favorable report of its action when taken by mouth in tertian and quartan malaria (Valenti and Tomaselli) has appeared. The author also reports on acetyloxyaminophenylarsinate of bismuth in very favorable terms, but it will be recalled that Anwyl-Davies found the preparation relatively ineffective in the treatment of clinical syphilis, a fact which suggests a guarded acceptance of the above-cited general therapeutic conclusions with regard to all these newer compounds.

OBSTETRICS

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Liver Extracts in the Toxemias of Pregnancy.—MILLER (*Atlantic Med. J.*, 1927, **31**, 141) reports 122 eclamptic and preëclamptic cases treated by hepormone. None of the preëclamptics developed convulsions and in 14 consecutive cases of eclampsia all recovered except 1 seen for the first time five days after onset of convulsions. The drug was administered intramuscularly and intravenously and the dosage depended on the severity of the condition. This is only a preliminary report but the author has never seen such persistently good results by any other treatment.

The Evaluation of Methods in Obstetric Analgesia and Anesthesia: With Special Reference to Gas Oxygen.—DAVIS (*Am. J. Obst. and Gynec.*, 1927, **14**, 806) finds that first-stage pain is relieved by hypodermic injection of heroin, $\frac{1}{2}$ gr., or pantopon, $\frac{1}{3}$ gr., and hyoscin, $\frac{1}{100}$ gr. Occasionally colonic ether oil is used. During second stage either gas oxygen or ethylene, which seems to be better than nitrous oxid, is used. Gas oxygen is satisfactory for most operative deliveries, except where a considerable degree of relaxation, as in version, is required.

An Ethical Consideration of the Indications for Cesarean Section.—FITZPATRICK (*Illinois Med. J.*, 1927, **52**, 458) concludes from his own observation and a perusal of the literature that there are many surgeons doing Cesarean sections for insufficient obstetrical indications. Many of these surgeons are not competent to perform the operations. He is not opposed to elasticity in the warrantable limitations but only to its unnecessary execution without even approximately justifiable indications.

Acute Appendicitis, Complicating Pregnancy, Labor and the Puerperium.—WILSON (*Surg., Gynec. and Obst.*, 1927, **45**, 620) reports 10 cases, about 80 per cent of cases occurring in the first six months; very rare in the last months. More common in puerperium than supposed, but is often overlooked. Primary attacks during pregnancy are rare. Pregnancy aggravates a diseased appendix. In late months of pregnancy the disease runs a rapid course in early perforation and peritonitis. Maternal prognosis is good if early operation is performed. In simple cases abortion is infrequent. If perforated 50 per cent will go into labor. The more advanced the pregnancy the greater the danger to mother and child. In the last month of pregnancy Cesarean section with appendectomy is advocated, the type of operation depending on the amount of infection.

The Safe Period as a Birth Control Measure.—DICKINSON (*Am. J. Obst. and Gynec.*, 1927, **14**, 718) concludes that there is no time of the month at which conception has not occurred in some women, but the premenstrual week is the relatively "safe period." There also occurs at this time a maximum sex desire, also a secondary wave of desire at the time of greatest fertility, that is, the week following menstruation. Ovulation, he believes, occurs between the fourteenth and nineteenth day from the beginning of the period.

Maternal Mortality in Canada.—MACMURCHY (*Canadian Med. Assn. J.*, 1927, **17**, 1434) compiled a special report for one year. The result showed a maternal mortality of 6 per 1000 living births, 1532 women dying in one year. Over 50 per cent had general poor health; in 190 cases the cause of death was given as cardiac disease complicating the pregnancy. Sepsis was the cause of death in 481 cases, or 27 per cent; hemorrhage, 357, or 23 per cent; toxemias, 344, or 22 per cent. Pituitrin was used in 327 cases, or 21 per cent, and in 3 of these rupture of the uterus occurred.

A Conservative Treatment for Chronic Endocervicitis.—BLAIR (*Canadian Med. Assn. J.*, 1927, **17**, 1480) criticises radical operation on the cervix before the menopause. He advises painting the cervix and entire vaginal vault with 2 per cent mercurochrome. This is also introduced into the cervical canal. The canal is dilated with a uterine dressing forceps. A powder, composed of kaolin, 2 parts, soda bicarbonate, 1 part, is then blown into the vagina by a Nassauer's siccator. He advises the cautery later for the erosions present.

Abortion, Its Prophylaxis and Treatment.—According to LITTLE and PERCIVAL (*Canadian Med. Assn. J.*, 1927, **17**, 1473), prevention of abortion includes a careful pelvic examination of patients giving a history of previous abortions and the correction of defects, such as retroversion, uterine fibroids and polyps. The authors advise the packing or the cervix with a gauze pack saturated in an oily solution of acriflavin to cause physiologic dilatation of the cervix followed by digital exploration.

GYNECOLOGY

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Irradiation of Cervical Cancer.—From the clinic of the late Dr. Franz in Berlin comes a report by WILLE (*Zentralbl. f. Gynäk.*, 1927, **51**, 2849) on the results of treatment of cases of carcinoma of the cervix. During the period 1915 to 1920 there were 190 patients treated by irradiation, while during the same time there were 375 patients operated upon for this condition, of which 358 were subjected to the Wertheim abdominal operation while 17 were treated by means of the vaginal hysterectomy of Schauta. In other words, in a series of 565 cases, 2 were operated upon to each 1 that was irradiated. Of the irradiation cases, 110 were treated with radium, 56 with Roentgen rays and 24 with the combination of radium and Roentgen rays. Of the 190 irradiated cases, 54 were considered in the operable stage, 21 in the borderline group and the remaining 115 were clearly inoperable. The most recent technique which was applied to the patients subjected to radium consisted of the application of 3500 mg. hours divided into two seances with one or two weeks interval between treatments. The results of irradiation showed a mortality of 3.73 per cent, due in all cases to peritonitis. Fistulæ occurred in 5.26 per cent of the cases, while burns including radium ulcers were observed in 4.74 per cent. Elevation of temperature following the irradiation occurred in 7.73 per cent of the series, including the cases which died of peritonitis. The following table gives the results very clearly:

	No. of patients.	Well after five years.
Operable cases:		
Radium	43	17 (39.53 per cent)
Radium and Roentgen ray	6	1
Roentgen ray	5	0
Total	54	18 (33.33 ")
Borderline cases:		
Radium	16	2 (12.50 per cent)
Radium and Roentgen ray	2	0
Roentgen ray	3	0
Total	21	2 (9.52 ")
Inoperable cases:		
Radium	51	1
Radium and Roentgen ray	16	2
Roentgen ray	48	0
Total	115	3 (2.61 per cent)
Grand total	190	23 (12.10 per cent)

It is of interest to note that the cases that they have listed as well and free from recurrence after five years have all been personally examined before their inclusion. Such an examination is not possible in some cases which live at a distance and a report by mail that the patient is well has not been accepted as evidence of freedom from recurrence. Particular emphasis is placed upon the very poor results which were obtained from the use of Roentgen therapy. The results obtained from radium irradiation are not quite so good as the best statistics which have been presented in this country, but probably represent those obtained in most of our good clinics. The most interesting part of these German reports is the fact that there is such a great amount of material available. This report, for example, which shows that 375 cases were deemed sufficiently early to be subjected to operation in the course of a few years, embraces a material which cannot be duplicated in this country.

Total Versus Subtotal Abdominal Hysterectomy.—It has been the experience of MASSON (*Am. J. Obst. and Gynec.*, 1927, **14**, 486) of the Mayo Clinic that the length of time involved in the performance of an operation has an important bearing on the results. Any operation that cannot be completed within an hour will be followed by more or less shock, which in itself predisposes to postoperative complications and high mortality. If total hysterectomy is performed only in simple cases, and if no attempt is made to remove the cervix at the primary operation in the presence of adnexal inflammatory disease or degeneration in a low-lying myoma, or again if the patient is obese, the risk should be but little more than that of the supracervical amputation. On the other hand, if total hysterectomy is performed only in the complicated and difficult cases, especially those in which there are complications as the result of inflammatory disease, the mortality and morbidity will be much higher. He is convinced that total hysterectomy should be performed by experienced surgeons in most cases in which hysterectomy is advisable and the patient is in good general condition. In the more difficult cases he is of the opinion that it is advisable to remove the body of the uterus with its associated tumors first; then by grasping the cervix with a tenaculum it can be much more easily removed secondarily. The subtotal operation, however, should be the operation performed by the occasional operator and the cervix should be removed only if it contains a definite lesion. As the experience of the surgeon increases he will, as a matter of course, remove the cervix at the primary operation in more cases. During the year 1926 total abdominal hysterectomy was performed in 229 cases in the Mayo Clinic, with 3 deaths, a mortality of 1.3 per cent. During the same year subtotal hysterectomy was performed 217 times, with 4 deaths, a mortality of 1.8 per cent. Statistics vary a great deal but in the hands of experienced surgeons the mortality of either operation should not be more than 2 per cent. Considering the fact that many of the patients are very anemic and others cachectic as the result of absorption from dengerating tumors or infection, the mortality is surprisingly low and, therefore, hysterectomy may be regarded as one of the safest of abdominal operations. During the preceding five years 29 cases of

carcinoma of the cervical stump have been observed in the Mayo Clinic. Twenty-one (72 per cent) of these occurred one year or more after the subtotal hysterectomy; 55 per cent occurred at least three years afterward and in 1 case there was an interval of fifteen years.

Papillary Cystadenoma of the Ovary.—It is very difficult for those of us who are called upon to remove a papillary cystadenoma of the ovary to give a definite prognosis. These tumors are usually considered benign with malignant possibilities, but just which ones will become malignant is the question that is frequently impossible to answer with any degree of accuracy. MAYFIELD (*Northwest Med.*, 1927, **26**, 236) has investigated the records of a series of 100 cases of this disease which were observed in the Mayo Clinic. He found that papillary cystadenoma varies in frequency from 16 to 18 per cent of all ovarian cysts. They are most probably developed, he believes, from epithelial structures derived from the germinal epithelium. Bilateral tumors are frequent, having been found in 43 per cent of the cases. He states that Roentgen ray and radium treatment should be given in addition to the operative procedure in every case in which implantation or metastasis is found. Even when it is not apparent that the tumor capsule is perforated recurrence may take place from unrecognized implants or metastases. Disregarding the degree of malignancy present, 44 per cent of the patients lived without recurrence of symptoms for an average period of seven years and seven months and 35 per cent of the patients died from recurrence within an average period of two years and two months after operation. The prognosis depends on whether the tumor capsule is perforated, the histologic evidence of malignancy of the tumor and the extent of the involvement of the surrounding tissues. The following figures are based on an interval of seven years and seven months after operation: If the capsule is perforated, and the malignancy of the tumor is of low grade, a 15 per cent chance of recurrence exists. If the capsule of the tumor is perforated, and the malignancy is of high grade, a 57.9 per cent chance of recurrence exists. In 10 per cent of the cases in the group with perforation of the capsule and tumors of a low grade of malignancy, death is caused by recurrence; in 75 per cent the patient survives without recurrence. In the group in which a tumor of a high grade of malignancy has perforated 50 per cent of the patients die from recurrence and 15.8 per cent live without recurrence. While the symptoms are variable and inconstant, there are in many cases certain points of similarity in the localization of the pain in the lower abdomen or pelvis, in its bearing-down character, its moderate severity and in the sensation of weight or fullness in the pelvis. This type of pain with a history of pelvic discomfort, menstrual irregularity, indefinite vesical or gastrointestinal symptoms, together with the presence of a rounded, firm, cystic tumor in the pelvis or abdomen is suggestive but not definite evidence of a papillary cystadenoma of the ovary. In 52.5 per cent of the cases investigated before the menopause there was some type of menstrual irregularity. Ascites was present in 31 per cent of the cases and usually indicated an advanced stage with perforation of the tumor capsule and peritoneal implants. The pre-operative diagnosis is always uncertain and the tumor is frequently mistaken for uterine fibromyoma.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Albuminuric Retinitis in One Eye, Embolism of the Central Retinal Artery in the Other.—BEAUMONT (*Brit. Med. J.*, 1927, i, 917) reports the case of a man, aged thirty-seven years, who suddenly lost the sight of the right eye twelve days before being seen by the author. The loss of vision in this eye was due to embolism of the central artery of the retina. He had suffered an attack of dimness in the eye a month earlier. Vision of the left eye was 6/6. A year later there was advanced atrophy of the disk and between the cherry-red macula and the disk there were small hemorrhages. A few months later the hemorrhages had disappeared and the atrophy was more pronounced. There was an evidence of cardiac or renal disease on repeated examination. The Wassermann reaction was negative. Six years later the patient was seen again by the author with a diagnosis of Bright's disease associated with right total and left partial loss of sight. On examining the right disk no evidences of retinitis were found. The left showed an intense neuroretinitis. The urine showed albumin and casts and the specific gravity varied daily between 1016 and 1020. No retinitis appeared in the right eye up to the day before his death. Autopsy revealed cardiac hypertrophy, mitral stenosis, slight coronary sclerosis and chronic granular contracted kidneys with profuse cystic degeneration of the cortex. The author explains the absence of retinitis in the right eye on the basis that atrophy and necrosis of the retina were followed by fibrosis.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Some Points in the Diagnosis and Localization of Brain Abscess.—Confining his discussion to brain abscess arising from aural suppuration and situated entirely within the dural membrane, SYMONDS (*J. Laryngol. and Otol.*, 1927, **42**, 440) states that in the early stages the symptoms are, as a rule, those common to retained pus elsewhere, such as fever, a rapid pulse, general malaise and anorexia. Headache may be prominent but is not commonly severe. This phase may lead directly to

an unrestricted suppurative encephalitis with rapid development of severe headache, vomiting and drowsiness, as the result of increased intracranial pressure. More commonly, the suppurative process becomes localized as an abscess cavity with tough walls through which there is a little septic absorption, the abscess producing signs and symptoms which depend upon its situation rather than its pathology. In this, the common variety of cerebral abscess, the signs of increased intracranial pressure are, in the early stages, limited to occasional headache, by no means always severe, but often experienced on waking and increased by stooping and coughing. Severe headache, vomiting, drowsiness and slowing of the pulse, when they develop in such a case, probably mark the occurrence of mechanical obstruction to the outflow from the ventricles with internal hydrocephalus. The author stresses the idea that such symptoms as headache, drowsiness, vomiting and slow pulse are no more the cardinal signs of this type of cerebral abscess than they are of cerebral tumor. The *localizing* signs of brain abscess, of course, depend on its situation. In cerebellar abscess, which is usually situated deeply within the lateral lobe, the symptoms are those of incoördination in the movements of the limbs on the same side, which is best shown in the upper limb and best demonstrated by the nose-finger test. The other sign of value is nystagmus, which can best be shown when the patient is asked to look toward the side of the lesion. In abscess of the left temporal lobe in a right-handed person, the localizing sign of outstanding value is asphasia. The other signs of temporal lobe abscess are common to both sides. They are the only signs of a temporal abscess on the right side in a right-handed person. Of these there are three of practical value—a slight weakness of the opposite side of the face, usually in the lower half; those signs attendant upon pyramidal tract pressure, as absent or diminished abdominal reflexes, increased tendon jerks or an extensor or doubtful plantar response; and defect in the visual field caused by involvement of the optic radiation. The cerebrospinal fluid is clear and contains a slight excess of cells—18 to 95 per c.mm.—and usually lymphocytes. A preponderance of polymorphonuclear leukocytes with diminution of chlorides and absence of sugar reduction is usually associated with clinical evidence of meningitis and means that the abscess is leaking either into the ventricular system or into the subarachnoid space. The author mentions the difficulty in distinguishing between certain cases of nonsuppurative encephalitis and brain abscess. Many of the points are exemplified by the histories of clinical cases.

A Clinical Consideration of Inflammations and Infections of Extratonsillar Pharyngeal Lymphoid Tissue Before and After Tonsillectomy.—By "extratonsillar pharyngeal lymphoid tissue," Wood (*Ann. Otol., Rhinol. and Laryngol.*, 1927, **36**, 511) refers more particularly to the scattered islands of lymph nodes on the posterior and lateral walls of the pharynx, exclusive of the adenoids. A dozen case reports are given to illustrate points brought out in the four classes into which he groups patients, from the standpoint of posttonsillectomic prognosis. His experiences have shown that inflammations and infections of extra-

tonsillar pharyngeal lymphoid tissue which has undergone a compensatory hypertrophy after tonsillectomy may be followed by the same focal infections that are so frequently attributed to the tonsils prior to their removal; that before tonsillectomy severe sorethroats occasionally occur in which inflammation is confined to extratonsillar lymphoid tissue of the pharyngeal walls without apparent involvement of the tonsil proper; that it is often possible to anticipate the degree of such pharyngeal inflammatory response following tonsillar removal if the entire pharyngeal picture is carefully studied and classified, inasmuch as patients showing a marked tendency to overdevelopment of this lymphoid tissue are prone to do badly after the tonsils are removed; that it is probable that infections originating in the paranasal sinuses frequently find their way into the blood stream through inflammation of the pharyngeal lymphoid tissue, either incited or fostered and fed by a postnasal discharge from the sinuses; that such nasal pathologic conditions as obstructions, sensitizations or infections play an important rôle in the production of pharyngeal inflammatory processes, both before and after tonsillectomy.

Pulmonary Abscess Following Tonsillectomy: Preliminary Report.—It is commonly accepted that a general anesthesia used for operations about the oral cavity predisposes to the development of a pulmonary abscess, but from statistics it is evident that a goodly percentage of these abscesses follow operations done under local anesthesia. Theoretically infection may be carried from the oral cavity by: (1) The lymphatic system; (2) the cardiovascular system; (3) the tracheobronchial tree. "Most has definitely proved that it is impossible for material to be transported from the tonsillar region to the lung by way of the lymphatics." Much clinical and experimental evidence has been produced to support both the "embolic" and "aspiration" theories of lung abscess formation, so that it would appear that pulmonary abscess can result from infected material entering the lungs from either the cardiovascular system or the tracheobronchial tree. Those who hold to the embolic theory have used as evidence against the aspiration theory the fact that this complication has occurred in as high as 19.3 per cent of cases tonsillectomized, using local anesthesia, believing apparently that the local anesthetic precludes the possibility of aspiration. However, OCHSNER and NESBIT (*Arch. Otolaryngol.*, 1927, **6**, 330) have proved that local anesthesia does interfere with the normal protective reflexes in over 600 cases of bronchography done according to the "passive technique," in which aspiration into the tracheobronchial tree occurred following the anesthetization of the pharynx. Believing that the same condition might be produced by a local anesthesia for tonsillectomy, those observers found on fluoroscopic examination that, in a series of 5 cases, so anesthetized by injecting 0.5 per cent of procain solution with epinephrin, attempts to swallow iodized oil resulted in its entry into the trachea and bronchi instead of into the esophagus. The authors believe that their observations supply the missing link of evidence in support of the aspiration theory.

RADIOLOGY

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Benign Tumors of the Stomach from the Roentgenologic Viewpoint. —Moore (*J. Am. Med. Assn.*, 1927, **89**, 368) draws deductions from 41 cases of benign tumor examined with the Roentgen ray at the Mayo Clinic and 52 cases recorded by others. As compared with malignant new growths, benign tumors of the stomach are rare, and compilations indicate that scarcely more than 1 per cent of the gastric tumors seen at operation are benign. Histologically the benign tumors are of great variety. They include myomas, adenomas, fibromas, papillomas, hemangiomas, lymphangiomas, myxomas, lipomas, chondromas, osteomas, mixed types, dermoid and miscellaneous cysts, and mucous polyps. Of these types, the mucous polyps, adenomas, papillomas, myomas, fibromas and hemangiomas are most common. The site of preference of benign tumors is in the pyloric or middle third of the stomach. As a rule, they project into the gastric lumen and are most often pedunculate but sometimes sessile. A small minority project outside the stomach and these also are usually pedicled. They are often quite small, but vary in size, are likely to be ovoid in shape and are subject to superficial ulceration. Single tumors predominate but most varieties may be multiple. Although at least primarily benign, almost any of them may become malignant. Exogastric tumors seldom produce gastric symptoms. Endogastric tumors of considerable size and smaller ones obstructing the pylorus give rise variously to epigastric distress, vomiting, melena, achlorhydria, increase of mucus, rarely hematemesis. Seldom is the tumor palpable. Secondary anemia is often the sole definite sign. The clinical diagnosis is likely to be ulcer or cancer. Roentgenologically exogastric tumors produce deformity of the gastric shadow which is likely to be misinterpreted as cancer or ulcer. Endogastric tumors have characteristics which should make the diagnosis possible in a high percentage of cases. The filling defect is usually central rather than marginal, smoothly and sharply outlined, and rounded or oval in shape. Screen examination with approximation of the gastric walls is necessary, as a rule, to reveal the tumors. The gastric outline is commonly preserved although it may be faint, the pedicle of the tumor may be traceable, the gastric wall is flexible, peristalsis is usually preserved, and the rugæ adjacent to the tumor are not obliterated as in cancer, or thrown into convergent folds as in ulcer. Multiplicity of the growths is strongly indicative of benignity; in classic examples of gastric polyposis the gastric shadow has the appearance of a coarse sponge. Growths confined to the antrum and obstructing the pylorus may be hard to distinguish from cancer or ulcer, but a benign growth which has prolapsed into the duodenal bulb produces a characteristic central bulbar defect.

Roentgen Diagnosis and Therapy of the Thymus in Children.—For the roentgenographic diagnosis REMER and BELDEN (*Am. J. Roent. and Rad. Ther.*, 1927, **18**, 119) recommend roentgenography by the flash method, making several exposures both in the upright and prone postures. The shadow of the enlarged thymus extends on both sides of the spine. Its borders are convex which is a point of distinction from tuberculous glands in the upper mediastinum. The shadow is wider below than above and merges with the shadow of the base of the heart. It is quite symmetrical on both sides and fits down over the base of the heart like a hat and this distinguishes it from a substernal thyroid, which is wider above than below. The shadow cast by tuberculous mediastinal glands is denser, and its borders convex: it is wide near the root of the lungs. Clinical symptoms of thymic enlargement include difficult breathing, choking, the peculiar crowing breathing and inability to swallow without lowering the head. For treatment one-tenth of an erythema dose of filtered, moderately high-voltage rays is given over front and back, repeating in a week or ten days, and, if necessary, continuing with longer intervals until four or five treatments are given. The writers are confident that the Roentgen ray offers not only a highly satisfactory method of treatment, but in practically all cases a safe and certain cure.

Roentgenologic Diagnosis of Coronary Sclerosis.—LENK (*Fortschr. a. d. Gebiete d. Roentgenstrahlen*, 1927, **35**, 1263) reports a case which was not clear clinically. Roentgenoscopic examination suggested the possibility of an aneurysm of the anterior wall of the left ventricle. However, a roentgenogram made with the Bucky diaphragm revealed a shadow stripe undoubtedly produced by a calcified coronary artery. This is the first time that coronary sclerosis has been recognized *in vivo* with the Roentgen ray, and it is possible that, with proper technique coronary sclerosis will be disclosed as readily as sclerosis of peripheral vessels.

Hypothyroidism.—According to POPE (*Arch. Phys. Therap., X-ray, Rad.*, 1927, **8**, 561), the various types of hypothyroidism may be divided into those of the preadolescent period and those of the postadolescent period. Children thus affected are often mentally retarded, are irritable, cry easily, have a disinclination to work or play, a tendency to adenoids and frequent attacks of tonsillitis, and an inordinate craving for sweets. Adults complain of physical and mental fatigue, are sensitive to cold, are good sleepers, lack activity, their upper lids tend to droop, they are likely to have a severe form of constipation, and they appear older than their years. Lowering of the basal metabolic rate is strongly confirmatory of the diagnosis. Treatment should begin with administration of thyroid gland, starting with small doses and increasing to larger. Physicians, as a rule, give too much thyroid extract. If a small dose is not effective iodin should be tried. For children there is nothing better than the old-fashioned syrup of the iodid of iron. Hydrotherapy is a valuable agent, following the application of heat (dry heat, steam, incandescent light baths), but the patient should not be made to perspire too freely. Mechanical massage, applied, not by a vibrator, but by larger, more efficient machines, is of service in increasing oxidation.

Rickets Occurring Late in Chronic Interstitial Nephritis.—KARSHNER (*Am. J. Roent. and Rad. Therap.*, 1927, **18**, 442) describes the case of a child suffering from chronic interstitial nephritis who exhibited clinically, pathologically and roentgenographically the characteristics of active rickets with onset at infancy and persistence until her death at nine years, in spite of intensive antirachitic measures. In an extensive literature such conditions are described under various names because of varying conceptions of its etiology and pathology. It constitutes a specific morbid entity of the malacic group of bone diseases, and is a rickets of renal origin. In 5 cases in which blood phosphorus and calcium determinations have been carried out, it is a low-calcium rickets. All cases of stunting of growth or late rickets should be examined carefully for nephritis, especially if operative correction of genu valgum or other deformity is contemplated. Conversely, chronic interstitial nephritis being a rarity in infancy and childhood, all such cases should be subjected to Roentgen examination of the bones for indications of rickets.

Supersoft Roentgen Rays in Dermatology.—Supersoft rays are Roentgen rays of extremely long wave lengths and large absorption coefficients. Their wave lengths average 2 Angström units and are of such low penetrative power that only a small percentage of them pass through the skin. For two years ELLER (*Am. J. Roent. and Rad. Therap.* 1927, **18**, 433) has employed them in the treatment of numerous skin diseases. Results were satisfactory in dermatophytosis, Duhring's disease, basal-cell epitheliomas, particularly of the eyelids, tinea capitis, verruca vulgaris, small keloids when treated early, neurodermatitis and sycosis barbæ. The results were less satisfactory in cases of acne vulgaris, acne keloid, angioma cavernosum, herpes zoster, lupus erythematosus, leucoplakia, parapsoriasis, psoriasis and lupus vulgaris. One case each of paronychia, rosacea, sarcoid and multiple flat epitheliomas was cured.

Retrograde Transport in the Colon.—LOSSEN (*Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1927, **36**, 562) describes an instance of retrograde transport of the opaque enema after cecosigmoidostomy. He describes it to point out the fact that the colon possesses the faculty of shifting its contents backward under normal conditions also. He is emphatic in stating that antiperistalsis need not be invoked to explain the phenomenon, for variations of tonicity in the different segments of the bowel are aufficient to produce it.

Emptying Mechanism of the Gall Bladder.—SCHONDUBE (*Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1927, **36**, 603), from his cholecystographic studies of the gall bladder in thin persons with marked concentrating power, concludes that evacuation of the gall bladder results from muscular contraction, and Graham's theory, that the evacuation takes place after the manner of a water pump, cannot be maintained. There is, first, an initial tonic contraction of the gall bladder, then a back flow of bile into the hepatic duct. The circular muscles contract first, then the longitudinal. Peristaltic movements could not be confirmed.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Role of Syphilis in the Parkinsonian Syndrome.—PARDEE (*Arch. Neurol. and Psychiat.*, 1927, **17**, 662) gives a brief review of the literature concerning cases in which the Parkinsonian syndrome and syphilis are concurrent. He emphasizes the acute aspects of encephalitis and the chronicity of neurosyphilis. He classifies the reported cases into two main groups. The first group is the larger and is made up of those cases in which a Parkinsonian syndrome, due to either encephalitis or arteriosclerosis, supervened on a syphilitic infection which may or may not have affected the central nervous system. He reviews 9 cases so far reported and adds 1 case in which the Wassermann reaction was 4 + with 1 cc. of spinal fluid and 2 + with 0.4 cc. The next group contains the cases in which no history of influenza or encephalitis is obtained. There are two subgroups: (1) Cases in which the diagnosis is confirmed by pathologic changes on postmortem examination and (2) cases in which the diagnosis is made by associated neurologic signs combined with positive serologic tests. The author reviews 4 cases reported in subgroup 1 and 6 cases in subgroup 2. He emphasizes this last group as that in which the presence of neurosyphilis expresses itself in a definite extra pyramidal syndrome. He adds 1 case. From the frequent scattered reports he concludes that the extrapyramidal syndrome is frequently associated with general paralysis. Treatment seems to be of little avail.

The Affective Nature of Illusion and Hallucination.—MILLER (*J. Neurol. and Psychopath.*, 1927, **8**, 1) states that illusion and hallucination are common in normal life in the course of ordinary conversation or in moments of reverie. He considers the processes as an integral part of the mental stream and lays a great deal of stress upon the subjective values and interpretations of the external world. He divides hallucinatory experience into two classes: Hedoniphoric hallucinations, which yield positive subjective states of satisfaction, and nociphoric hallucinations, which bring about subjective states of distress. He cites a number of his own cases and cases from the literature to demonstrate that lilliputian and brobdignagian hallucinations are associated with pleasant and unpleasant effects respectively. He would explain this, as well as the alternation of the two types in some cases on the basis of childhood complexes *en rapport* with the size of persons seen or imagined. The one corresponds with the fear inspired by the adult and the other the joyful sense of security obtained by living in a reduced universe. If one regresses to the infantile level of experience for satisfaction he must be prepared to revive also the infantile sense of guilt.

A Clinical Analysis of an Extrapyramidal Syndrome; Paralysis Agitans and Postencephalitic Parkinsonism.—YOUNG (*J. Neurol. and Psychopath.*, 1927, **8**, 9) analyzes 50 cases of Parkinsonian syndrome, 39 of which were of postencephalitic origin and 11 belong to the idiopathic group. There were 34 males and 16 females. The study is too detailed for complete abstraction here. Among the most important findings were the following: Ages of postencephalitics varied from nine years to the fifth decade, 26 occurring between the ages of twenty and forty. The fifth and sixth decade was the average age period of the idiopathic cases. The average duration of Parkinsonism in postencephalitis was two years and two months, ranging from three months to seven years. In the idiopathic group the average was two years and eleven months, ranging from nine months to six years. Analysis of the signs and symptoms in detail show them all, with the exception of loss of pupillary reaction to light, occurring frequently enough in both groups to make them of doubtful value in differential diagnosis. The loss of the pupillary reaction occurred only in the postencephalitic group. The objective signs in general occurred more frequently in the postencephalitic group. The author concludes that as to the synergic action of muscle groups in Parkinsonism there is no departure from normal physiologic law; that associated movements are not lost but that some associated movements are present that are not seen in the normal individual, and that absence of arm swinging in walking is the one almost constant associated movement that is lost.

Social Adjustment of Retarded Children.—KINDER and RUTHERFORD (*Ment. Hyg.*, 1927, **2**, 811) present a follow-up study from January to June, 1926, of retarded children seen in the Henry Phipps Psychiatric Dispensary between January and June, 1921. The ages on admission to the clinic range from two to fifteen years, all but 8 of the cases being between seven and fifteen. Organic and frankly psychotic cases were excluded, as were also the few cases of colored children. None of the cases had had the advantage of any sort of special training prior to the first examination nor did special training during the subsequent five years enter as a factor in the social adaptation studied. The study began with 97 cases, but 29 of these could not be located. Of the 68 remaining, 27 were girls and 41 boys. All of the cases under seven years of age were so severely retarded as to be custodial in character. There were 4 boys and 4 girls in this group. For the remaining 60 cases the original I. Q. findings were used as the basis for classification of the children. The data for the investigation were secured on five points: (1) The retardation of the child; (2) the environmental setting in which the child had lived and his adjustment at the time of the first visit to the dispensary; (3) the environmental setting during the five years between the first visit and the present study; (4) the social adjustment at the time of the present study; (5) the school record. A detailed analysis is made along these lines and a number of type cases are presented. The results indicate quite clearly that the environmental factors are of much greater influence in the social adjustment of retarded individuals than has previously been recognized. There was relatively little correlation between the degree of retardation and social adjustment of the entire group of children only 14 made satisfactory adjust-

ments and of these about one-third came from good or average homes while two-thirds came from environments that were poor or very poor. Twenty of the children studied had been placed in environments that offered opportunities superior to those in which they had previously lived. Twelve of the 14 individuals mentioned above belonged to this group. Over half of the cases were or had recently been inmates of institutions. The defectives were custodial cases. Of the other groups, 18 of the 28 institutional cases were corrective and only 10 custodial. The authors conclude that the child's environment must be considered as an important contributing factor in any study of the social adaptation of retarded children.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Rhythmic Range of the White Blood Cells in Human, Pathologic Leukopenic and Leukocytic States, with a Study of Thirty-two Human Bone Marrows.—It is a well-known fact that unexplainable inconsistencies frequently occur in clinical blood counts. DOAN and ZERFAS (*J. Exp. Med.*, 1927, **46**, 3) have done an exhaustive series of blood counts upon 20 clinical cases of a varied nature, in addition to which differential cell counts of bone marrow were done upon cases coming to autopsy at the Boston City Hospital. From these an interesting series of tables and graphs have been assembled, containing figures on total white cell counts, total red cell counts, hemoglobin, hematocritic and serum protein values. Patients were followed as a routine at fifteen-minute intervals for periods of three hours, certain cases being observed on successive occasions for similar periods. One may briefly summarize their results as follows: Serum protein values are most constant, there being little or no variability in the serum protein content under normal basic fasting conditions. The variations found in clinical cases in total white cell counts revealed wide fluctuations, comparable with those found in normal physiologic states. The granulocytes follow a more or less hourly rhythm the most marked shift in the Arneth pattern and moment of greatest percentage motility corresponding to the peaks. The authors found complete independence between the concentration of individual types of white and red cells in the peripheral circulation, which seems to indicate separate physiologic mechanisms of control for each type of cell. The various factors involved in making a blood count necessarily leave single observations open to grave misinterpretation. The clinical value of blood counts must, therefore, come from repeated readings over longer or shorter periods in consecutive counts. A zonal concept for both red and white

counts with adequate extremes should be kept in mind for both physiologic and pathologic states. The remarkable reciprocity between the myelocytes and the mature polymorphonuclear leukocytes found to exist in bone marrow, together with the periodicity of fluctuation of neutrophils in the peripheral circulation, leads to the formulation of the hypothesis of a constant functional withdrawal of granulocytes, from the peripheral circulation, with periodic delivery of new cells from the bone marrow.

On the Origin of Reticulin Fibrils.—In further studies on the origin of reticulin fibrils Foot (*Am. J. Path.*, 1927, **3**, 401) performed a series of experiments, using fresh granulation tissue, muscle, liver, spleen and lymph nodes from rabbits as well as "whole blood cultures," from which he draws the following conclusions: Reticulin fibrils are not artefacts and preëxist in the tissues. On the other hand, collagen fibrils may be artefacts, as the use of Zenker's fluid as a fixative solution resulted in the coagulation of blood serum and tissue juices with the appearance of structures closely resembling collagen fibrils. The relation of reticulin and collagen is not definitely known. It seems probable that collagen is a colloidal or semifluid substance that can be coagulated into granules or a semblance of fibrils by the action of fixative fluids, especially Zenker's solution. It is suggested that this substance impregnates fibrils or tissue strands rather than forming fibrils of its own. The fibrils so formed lose their affinity for silver, and stain with acid fuchsin. This would serve to explain the presence of fibrils staining partially with silver and partially with acid fuchsin. The source of reticulin in the body tissues is still a matter for speculation. In "cultures of the whole blood," however, the reticulum of laked erythrocytes gives rise to reticulin fibrils. That the fibrils so formed have no relation to fibrin is proven by the use of defibrinated blood with the production of a similar result. No claim is made that the source of reticulin formation has been found, but that "a new and novel aspect of fibril formation has been presented" which not unlikely bears a close relation to that process in granulation tissue and tumors.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Comparison between Multiple Cases of Measles, Scarlet Fever and Infantile Paralysis.—Aycock and Eaton (*Am. J. Hyg.*, 1925, **5**, 733), in attempting to evaluate facts for infantile paralysis found in a previous study, have made a comparison with scarlet fever and

measles, the former chosen because of its short incubation period, and the latter because of its longer incubation period. The data are from Providence and represent 3098 families which had multiple cases of scarlet fever (1887–1916) and 2589 families which had multiple cases of measles (1916–1923). The data presented show that secondary cases of measles usually occur ten to twelve days after the onset of the initial case in the family and that third cases occur, as a rule, simultaneously with the second case. This indicates that the majority of multiple cases are derived from the initial case. Since the interval between the initial case and subsequent cases corresponds to the incubation period of the disease, it may be stated that multiple cases, as a rule, are contracted from the initial case at about the time of onset. Scarlet fever acts similarly except that, the period of incubation being short, secondary cases overlap common source cases, making analyses of the curve more difficult. Unlike measles, scarlet fever has a relatively large number of late secondary cases, doubtless due to a prolonged period of infectivity. It thus appears that measles and scarlet fever are both introduced into the family by the initial cases from which after the onset of the disease, the infection is transmitted to other members of the same family. That is, the initial case may be considered the source of the family outbreak. Infantile paralysis when introduced into a family acts quite differently. Only exceptionally do multiple cases occur, and when this happens they usually come down within a short time of each other, indicating simultaneous infection. In this respect, multiple cases of infantile paralysis resemble second and third cases of measles. This indicates that contact infection during the acute stage does not play the same role in this disease as in measles or scarlet fever, but that the virus of infantile paralysis enters the family in such a way that in the few instances where more than one member is infected, this is accomplished practically simultaneously.

The Care for the Unborn Child.—EDEN (*Lancet*, 1925, 1153) states that in considering the chances of a child being born alive, it will be found that there are no official figures on miscarriages. Dr. Amand Routh has estimated, however, from the experience of clinical observers and from figures of certain United States cities that almost 1 in 5 pregnancies terminate in miscarriage. Regarding still births, there is more information available. In England and Wales, in 1924, the stillbirth rate was 3.3 per cent of live births. The total maternal mortality was 3.7 per 1000 live births, so that the stillbirth rate alone was about ten times the total maternal mortality. In France, in 1922, the proportion of registered stillbirths amounted to 44 per 1000 live births, being 93 in Paris, 69 in a group of large towns and only 26 in rural departments. It is here shown that the great centers of population have the highest stillbirth rate. Intrauterine life maybe divided into three periods: The embryonic period, from the act of fertilization to the eighth week; the fetal period, from the end of the eighth week to the onset of labor; the intranatal period, comprising the birth process itself. In the embryonic stage malformations are initiated. Experiments upon the lower animals lead us to believe that the cause

of malformations in man must be sought in some alteration of environment which would be comparable to the physical or mechanical stimuli used in these experiments. Traumatism, alterations of nutrition, nondevelopment of the pituitary body produce malformations. Little is known of the actual causes of death in the embryonic period, but it is probable that a considerable number of miscarriages are due to a certain unfitness of the early embryo to complete its development. Experiments show that in all creatures the reproductive process is attended by a certain amount of wastage. In studying the fetal period, the question of the transmission of immunity is of interest. Experiments on the antitoxin of diphtheria show that the immunity of the newborn infant is brought about by the transplacental distribution of the antitoxin present in the mother's blood, and that the amount of antitoxin is the same in both the mother's and the child's blood. Kleinoff claims to have shown that the umbilical blood of the newborn child possesses definite hemolytic or bacteriolytic powers. Another question pertaining to the well-being of the child at birth is the effect of maternal occupation on the child. Pinard has shown that women who ceased work from one to three months before confinement had heavier babies than those who were industrially occupied in sitting positions up to confinement and much heavier than those who were occupied in standing positions up to confinement. Le Tourner found that women who were admitted to the clinic before labor had the heaviest babies, those who ceased work for at least ten days had babies of less weight and those who worked up to confinement had the smallest babies. Fuchs excluded all premature infants from his inquiry and observed the following: (1) That the infants of factory workers are smaller than those of the other classes; (2) that the infants of all classes benefit by a hospital régime during the latter weeks of pregnancy; (3) that especially women who work in factories, and to a less extent town workers generally, benefit more from the hospital régime than do women engaged in outdoor agricultural occupations. The effect of maternal privation and hardship is seen from Professor Klotz's figures on the average birth weights before and after the war for legitimate and illegitimate births. The legitimate infants showed no differences in weight between the prewar and postwar years, but the illegitimate infants showed a much smaller birth weight in the postwar years of hardship and privation. Still births in France taken over the period 1912–1921 show the highest rates during the years 1916–1919. Regarding the effect of diet on the development of the fetus, several suggestive studies by Reynolds and Macomber have been published. Experiments were conducted on the manner in which the fertility of rats could be influenced by feeding on specifically deficient diets. Bell found the calcium content of the diet of an expectant mother especially deserving of attention.

The Problem of Fetal and Neonatal Death.—STERLING (*U. S. Pub. Health Rep.*, 1927, **42**, 717) made a study of stillbirths and deaths during the first month in the registration area for the year 1924. There were a total of over 150,000, nearly evenly divided between fetal and neo-

natal deaths. In recent years there has been a pronounced fall in all infant death rates, but only a slight fall in those classed as neonatal. In studies where careful investigations have been made syphilis, dystocia, toxemia, malformation and prematurity account for a large majority of all fetal deaths. Among deaths during the first months, prematurity, birth injuries and congenital malformations are most important. Syphilis is of very small moment. It appears that poverty and poor sanitary surroundings have little or no influence on neonatal mortality, though of some importance later. Employment of the mother seems to be not important unless the employment is away from home. The racial stock seems to be of considerable importance, Russians and Italians having decidedly better figures than other racial stock. The urban neonatal death rate is somewhat higher than the rural, though no satisfactory explanation is at hand. The use of forceps is suggested as adversely affecting the chances for survival of the child. The third decade seems to be the most favorable age for maternity. Illegitimacy is associated with a high neonatal death rate. Alcoholism of the mother is unfavorable but how much of the adverse influence is due to alcohol and how much to associated influences. The paper closes with the following quotation: "The solution of the infant mortality problem calls for something besides appropriations for intensive child-welfare work. We should honestly face the probability that unknown factors are affecting the value of much of our infant and child-welfare work."

A Survey of Venereal Disease Prevalence in Detroit.—National and Local Organizations (*Pub. Health Repts.*, 1927, **42**, 1760) coöperated in securing data through the use of questionnaires filled out by physicians and institutions. The syphilis rate was found to be 6.98 per 1000 population, and the gonorrhea rate 6.5 per 1000. As to the trend of venereal disease incidence, the opinions of physicians were conflicting, but the majority regarded the diseases on the increase while the local health authorities regarded them as decreasing.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 20, 1928

The Activity Coefficients of the Carbonate and Bicarbonate Ions.—W. C. Stadie and E. C. R. Hawes (from the Department of Research Medicine, University of Pennsylvania). The activity coefficients of the bicarbonate and carbonate ions were determined by means of the hydrogen electrode in a series of solutions containing varying concentrations of sodium chlorid up to 5 moles per liter. It was found that the ion

activity coefficients followed the law of Debye for concentrated solutions. Further a comparison with the values of Walker, Bray and Johnston showed that the fundamental assumption made in determining pH by the hydrogen electrode, namely, the liquid junction, is warranted.

Vasodepressor Substance in the Liver After Bile-duct Obstruction.—I. S. Ravdin (from the Department of Research Surgery, School of Medicine, University of Pennsylvania). In attempting to find a satisfactory explanation of the vasodepressor state which occurs at times after the release of obstruction of the common bile duct, liver extracts from obstructed dogs were prepared after the method described by Best, Dale, Dudley and Thorpe. The amount of the depressor substances, probably histamin and cholin, was in excess of that extracted from normal liver, but the actual content varied. The extracts were assayed by estimating their effect on the blood pressure of the cat before and after the administration of atropin and by their effect on the uterus of virgin guinea pig.

Physiologic and Physical Study of Photic Urticaria.—S. E. Pond (from the Department of Physiology, University of Pennsylvania). A series of experiments designed to test the skin sensitivity to radiant energy have led to a means of determining the threshold of an urticarial reaction which is constant within a considerable range of variation of external and bodily conditions. Over a period of four years the general reaction and the threshold of an urticarial wheal was found to be the same both as to frequency and quantity of radiant energy absorbed by the skin. No difference in threshold or in type of reaction was found over the entire body surface except on calloused and scarred areas. On the latter no reaction was ever evoked. On calloused areas the reaction was limited and not easy to determine. The reaction was measured as to time of appearance of an arbitrary difference in reflection coefficient between the wheal area and the adjacent skin. The wheal was always found to be self limited and never extended beyond the area exposed to the monochromatic beam. Subthreshold exposures of long duration to exhaust any sensitizer of a labile nature were without effect except for a few moments after exposures. Following second-degree burn the reaction was abolished for several weeks. After apparent recovery of the skin the same threshold for the reaction was again found. No sensitizer of a photodynamic nature has been isolated, although tests were made to locate such. Porphyrins were not found in any case and acetylsalicylate sensitization was not proven. Freedom from allergic and from protein sensitization was established. No other physical cause than the band of radiant energy between 3000 and 3400 Angström units was found to effect the wheal. Within certain limits the Bunsen-Roscoe relation was found to hold; that is, between 10 cm. and 4 m. from the radiator, $It = k$.

The Effects of Certain Anesthetics on the Cleavage Reaction in Arbacia Eggs.—R. Blumenthal (from the Department of Zoölogy, University of Pennsylvania). The following were used as anesthetics: $\frac{N}{100}$ to $\frac{N}{1000}$ KCN, 5 per cent methyl cyanid, 1.5 per cent ethyl acetate,

3 per cent isopropyl alcohol, 3 per cent n-propyl alcohol, 10 per cent methyl alcohol. The main conclusions follow: Anesthetized eggs can be fertilized while in that condition. Fertilized and unfertilized arbacia eggs exposed to KCN in concentrations varying from $\frac{N}{100}$ to $\frac{N}{1000}$ and then transferred to normal sea water, show a delay in cell division beyond that of control eggs, the amount of delay depending upon the concentration of KCN used but independent of the length of exposure to these concentrations up to sixty minutes. Fertilized arbacia eggs are more susceptible to KCN than are unfertilized eggs. This susceptibility is demonstrated by the greater delay in cell division which occurs in the case of the fertilized eggs. Fertilized and unfertilized arbacia eggs exposed to the alcohols, methyl cyanid and ethyl acetate exhibit no delay in cell division upon transference to normal sea water. Fertilized eggs are more susceptible to these anesthetics also, but this susceptibility is shown by a hastening in cell division beyond that of control eggs. Length of exposure of fertilized and unfertilized eggs to these anesthetics has no specific effect upon time for first cleavage to occur. All the anesthetics employed, except ethyl acetate, do not inhibit the formation of fertilization membranes. Sperm are more resistant to the anesthetics that are eggs, but they can be anesthetized. Even though the eggs are in a condition of anesthesia, a certain amount of internal development can be seen. It is suggested that this development has to do with mitotic processes. It is suggested that KCN causes two distinct reactions simultaneously. The first, that of inhibiting cell division (anesthesia), and the second, that of inhibiting oxidation. It is indicated that anesthesia is not the direct result of the inhibition of oxidation. A distinction is made between the process of fertilization membrane formation and the processes leading up to cell division. The former, which is not inhibited by anesthetics, is thought of as a mechanical process and the latter as a physiologic process.

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